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#### (54) 【発明の名称】末端分枝高分子リンカーおよびそれを含む高分子複合体

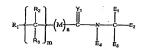
# (57)【要約】

多数のローディングが可能な末端分枝高分子プロドラッ グブラットフォームを開示する。本名別の好まとい意様 では、プロドラッグブラットフォームは活性数でを している各分柱がベンジル原順反応を受けた後を多数の 駅化合物を放出する。プロドラッグの製造方法もよび哺 乳類の治療におけるその使用方法もまた開示する。1つ の好ましい態様では、式(1)などの高分子複合体を提供 する。

【特許請求の範囲】 【請求項1】

: 左 【化1】

(II)



(式中、

R,は高分子残基であり; Y, はO、SまたはNR, であり; MはO、SまたはNR、であり: E, は

【化2】



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であり: E2-4は独立に、H、E、または [4k 3 ]

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であり;

(a) は0または1であり;

(m)は0または正の整数であり;

(n)および(p)は独立に、0または正の整数であり;

Y<sub>2-3</sub>は独立に、O、SまたはNR<sub>4</sub>。であり;

 $R_{2-10}$ は独立に、水素、 $C_{1-6}$ アルキル、 $C_{2-1}$ 分枝鎖アルキル、 $C_{3-6}$ シクロアルキル、 $C_{3-6}$ 40 置換アルキル、C3-8置換シクロアルキル、アリール、置換アリール、アラルキル、C3-6へ テロアルキル、置換C.-。ヘテロアルキル、C.-。アルコキシ、フェノキシおよびC.-。ヘテロ アルコキシからなる群から選択され; D.およびD.は独立に、OH、

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[1L4]

(式中,

(v)および(t)は独立に、0または約6までの正の整数であり;

JはNR, または 【化5】

M

\$ \$

であり;

L、およびL、は独立に選択された二官能性リンカーであり;

Y<sub>4-</sub>,は独立に、O、SおよびNR<sub>4</sub>からなる群から選択され;

 $R_{1,1,4}$ は独立に、水素、 $C_{1,6}$ アルキル、 $C_{1,1,5}$ 分枝鎖アルキル、 $C_{1,8}$ シクロアルキル、 $C_{1,6}$  置換アルキル、 $C_{1,6}$  でデロアルキル、 $C_{1,6}$  でデロアルキル、置換 $C_{1,6}$  へテロアルキル、 $C_{1,6}$  でデルコキシ、フェノキシおよび $C_{1,6}$  へテロアルコキシからなる群から選択され:

Arは式(I)に含まれる場合に多置換芳香族炭化水素または多置換複素環基を形成する成分

であり;

B,およびB,は独立に、脱離基、OH、ヒドロキシル基含有成分またはアミン基含有成分の残 基からなる群から選択される)

または末端分枝基である}

で表される化合物。

【請求項2】

R, が水素、NH, 、OH、CO, H、C, \_ a 基および

[116]

$$E_2 = \begin{bmatrix} E_1 & & & & \\ & & & & \\ & & & & \\ E_3 & & E_4 & & \end{bmatrix} \begin{bmatrix} & & & & \\ & & & \\ & & & \\ & &$$

からなる群から選択されるキャッピング基Aをさらに含んでなる、請求項 1 に記載の化合物。

【請求項3】

式: 【化7】

$$E_2 = \underbrace{\begin{bmatrix} \vdots \\ X_1 \end{bmatrix}}_{E_3} \underbrace{\begin{bmatrix} X_1 \\ X_2 \end{bmatrix}}_{E_4} \underbrace{\begin{bmatrix} X_2 \\ X_1 \end{bmatrix}}_{E_4} \underbrace{\begin{bmatrix} X_1 \\ X_2 \end{bmatrix}}$$

で表される、請求項2に記載の化合物。

【請求項4】 上記末端分枝基が式:

[化8]

|式中、 |**5**,は

【化9】

であり;

E, c.\_, a は独立に、H、E,, または 【化10】

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であり:

(n)および(p)は独立に、0または正の整数であり;

Y, 、は独立に、O、SまたはNR。であり;

R<sub>8-10</sub>は独立に、水素、C<sub>1-6</sub>アルキル、C<sub>3-12</sub>分枝鎖アルキル、C<sub>3-8</sub>シクロアルキル、C<sub>1-6</sub> 置換アルキル、Cana置換シクロアルキル、アリール、置換アリール、アラルキル、Cana テロアルキル、置換C.-6ヘテロアルキル、C.-6アルコキシ、フェノキシおよびC.-6ヘテロ アルコキシからなる群から選択され;

D', およびD', は独立に、OH、

[(E11]

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または [/L 1 2 ]

(式中、

(v)および(t)は独立に、0または約6までの正の整数であり;

L およびL は独立に選択された二官能性リンカーであり;

Y<sub>4-7</sub> は独立に、O、SおよびNR、からなる群から選択され;

R1-14は独立に、水素、G-6アルキル、C3-12分枝鎖アルキル、C3-6シクロアルキル、G-。置換アルキル、G.。置換シクロアルキル、アリール、置換アリール、アラルキル、G.。 ヘテロアルキル、置換G - 5ヘテロアルキル、G - 5アルコキシ、フェノキシおよびG - 5ヘテ ロアルコキシからなる群から選択され;

Arは式(I)に含まれる場合に多置換芳香族炭化水素または多置換複素環基を形成する成分 であり:

B、およびB、は独立に、脱離基、OH、ヒドロキシル基含有成分またはアミン基含有成分の残 基からなる群から選択され; 長、は

【化13】



であり;

E<sub>46-48</sub>は独立に、H、E<sub>4</sub>,または 【化 1 4】



(式中、

D",およびD",は独立に、OH、

【化15】

または 【化16】

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & \\ & & \\ &$$

である) である}

である]

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で表される、請求項1に記載の化合物。
 【請求項5】
Y,が0である、請求項3に記載の化合物。
 【請求項6】
Rがポリアルキレンオキシド残基を含んでなる、請求項1に記載の化合物。
 【請求項7】
Rがポリエチレングリコール残基を含んでなる、請求項6に記載の化合物。
【請求項8】
Rがポリエチレングリコール残基を含んでなる、請求項3に記載の化合物。
【請求項9】
                                                                                    10
凡が
-C(=Y<sub>6</sub>)-(CH<sub>2</sub>), -0-(CH<sub>2</sub>CH<sub>3</sub>O), -A
-C(=Y, )-Y, -(CH, ), -0-(CH, CH, O), -A.
-C(=Y, )-NR, , -(CH, ), -O-(CH, CH, O), -A.
-(CR, 4R, , ), -0-(CH, ), -0-(CH, CH, O), -A,
-NR, , -(CH, ), -O-(CH, CH, O), -A.
-C(=Y, )-(CH, ), -O-(CH, CH, O), -(CH, ), -C(=Y, )-,
-C(=Y, )-Y, -(CH, ), -O-(CH, CH, O), -(CH, ), -Y, -C(=Y, )-,
-C(=Y_{6})-NR_{2}, -(CH_{2})_{6}-O-(CH_{2}CH_{3}O), -(CH_{3})_{6}-NR_{2}, -C(=Y_{6})-C(=Y_{6})_{7}
-(CR, 4R, 5), -0-(CH, 2), -0-(CH, CH, 0), -(CH, ), -0-(CR, 4R, 5), -, $$ $ $
                                                                                    20
-NR, , -(CH, ), -0-(CH, CH, O), -(CH, ), -NR, , -
(式中、
Y.およびY.は独立に、O、SまたはNR。であり:
xは重合度であり:
R<sub>3</sub>、R<sub>4</sub>およびR<sub>2</sub>,は独立に、H、C<sub>4</sub>,アルキル、C<sub>4</sub>,分枝鎖アルキル、C<sub>4</sub>,シクロアル
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Q-6ヘテロアルコキシからなる群から選択され; eおよびfは独立に、0、1、または2であり:かつ

Aはキャッピング基である) からなる群から選択される、請求項6に記載の化合物。

【翻求項 1 0 】 R, が-O-CCH, CH, O), を含んでなり、かつxは重量平均分子量が少なくとも約20,000であるような正の整数である、請求項 9 に記載の化合物。

キル、 $C_{1-6}$ 置換アルキル、 $C_{1-6}$ 置換シクロアルキル、アリール、置換アリール、アラルキル、 $C_{1-6}$ ヘテロアルキル、置換 $C_{1-6}$ ヘテロアルキル、 $C_{1-6}$ アルコキシ、フェノキシおよび

【請求項111

R の重量平均分子量が約20,000~約100,000である、請求項3に記載の化合物。 【請求項12]

『 の重量平均分子量が約25,000~約60,000である、請求項3に記載の化合物。 『 請求項13】

式

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【化17】

で表される、請求項3に記載の化合物。

【請求項14】 D<sub>i</sub> が

【化18】

である、請求項13に記載の化合物。

【請求項15】

D<sub>i</sub>が

[1E19]

である、請求項13に記載の化合物。

【請求項16】

L, が(CH, CH, O), である、請求項1に記載の化合物。

【請求項17】

L, 25-CH, -, -CH(CH, )-, -CH, C(O)NHCH(CH, )-, -(CH, ), -, -CH, C(O)NHCH, -, -(CH, ), -NH-、-(CH, ), -NH-C(0)(CH, ), NH-および-CH, C(0)NHCH(CH, CH(CH, ), )-からなる群から選択され 50 る、請求項1に記載の化合物。 【請求項18】 【化20】

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および 【化21】

【式中、 R, はPEG残基であり、かつDは

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# [1222]

HN~~~

(式中、

Bはアミンまたはヒドロキシル基含有薬物の残基である)

からなる群から選択される}

からなる群から選択される、請求項1に記載の化合物。

【請求項19】

Bがダウノルビシン、ドキソルビシン; p-アミノアニリンマスタード、メルファラン、Ara -((シトシンアラビノシド)、ロイシン-Ara-(、およびゲムシタビンからなる群のメンバー の残基である、請求項 18 に記載の化合物。

【請求項20】

治療が必要な哺乳類に、有効量の請求項1に記載の化合物(式中、D<sub>1</sub>は生物学上活性な成分の残基である)を投与することを含んでなる、治療方法。

【請求項21】

治療が必要な哺乳類に有効量の請求項18に記載の化合物を投与することを含んでなる、 40 治療方法。

【請求項22】

Arが式:

# [12 4 ]

#### (士中、

 $R_1$ :および $R_{1-1}$ 。は独立に、水素、 $C_{-6}$ アルキル、 $C_{-1}$ :分枝鎖アルキル、 $C_{-6}$ :シクロアル 10 キル、 $C_{-6}$  置換アルキル、 $C_{-6}$  置換シクロアルキル、アリール、置換アリール、アラルキル、 $C_{-6}$ アルコキシ、フェノキシおよび $C_{-6}$ 0、テロアルキル、ので、 $C_{-6}$ 0、テロアルコキシからなる群から選択される)

# で表される、請求項1に記載の化合物。

# 【請求項23】

R. およびR. . - . 。が各々、HまたはCH, である、請求項22に記載の化合物。

# 【請求項24】

高分子複合体の製造方法であって、

# 式(III):

[1] 2 5 ]

#### (式中、

(v)および(t)は独立に、Oまたは約6までの正の整数であり; JはNR,または

# [12 6]

# であり;

L およびL は独立に選択された二官能性リンカーであり;

Y4-5は独立に、O、SおよびNR、からなる群から選択され:

 $R_{1-1}$ , は独立に、水素、 $C_{1-6}$ アルキル、 $C_{1-1}$ 分枝鎖アルキル、 $C_{1-6}$ シクロアルキル、 $C_{1-6}$ でで、で、アリール、潜換アリール、アラルキル、 $C_{1-6}$ で、アレフトキル、 $C_{1-6}$ で、ヘテロアルキル、 $C_{1-6}$ で、ヘテロアルキル、 $C_{1-6}$ で、ハテロアルコキシ、フェノキシおよび $C_{1-6}$ 、ヘテロアルコキシからなる群から選択され、

Arは式(I)に含まれる場合に多置換芳香族炭化水素または多置換複素環基を形成する成分 50

であり:かつ

B', はヒドロキシルまたはアミン基含有成分の残基である)

で表される化合物と、式(IX):

【化27】

$$R_1 = \begin{bmatrix} R_2 \\ C \\ R_3 \end{bmatrix}_{m} \begin{bmatrix} Y_1 \\ C \\ R_6 \end{bmatrix}_{E_6} \begin{bmatrix} E_5 \\ E_6 \end{bmatrix}_{E_7}$$

(式中、

E, は

【化28】



であり;

E。は独立に、H、E、または

[1k.2 9]

であり・

D,およびD,は独立に、CH、保護されていないアミンまたはヒドロキシルと反応しうる脱離 30 基、または末端分枝基であり:

R は高分子残基であり;

Y, dO、SまたはNR、であり、

MはO、SまたはNR、であり:

MはU、SまたはNR、であり;

(a)は0または1であり;(m)は0または正の整数であり;

(n)および(p)は独立に、Oまたは正の整数であり;

Y, , は独立に、O、SまたはNR, であり;かつ

□ スプン アン・スーター アン・スーター アルコキシ、フェノキシおよび C. - ヘテロアルコキシ、フェノキシおよび C. - ヘテロアルコキシからなる群から選択される)

で表される化合物とを、高分子複合体を生成させるのに十分な条件下で反応させることを 含んでなる、上記方法。

【発明の詳細な説明】

【技術分野】

[0001]

本発明は生物活性材料の長時間作用性複合体の作製に有用である新しいタイプの末端活性 化高分子材料に関する。特に、本発明は治療的ペイロードの高い高分子系複合体およびそ の製造方法に関する。

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【背景技術】

[0002]

長年にわたり、生物学上有効な材料を哺乳類に投与するいくつかの方法が提案されてきた。多くの薬剤が水溶性塩として入手可能であり、比較的容易に医薬製剤に配合することができる。所望の薬剤が液体に不溶性である場合、またはin vivoで急速に分解される場合には問題が起こる。特に、アルカロイドは難溶である場合が多い。

[0003]

薬剤を可溶性にする1つの方法がそれらを可溶性プロドラッグの一部として含める方法である。プロドラッグは投与した際にin vivoにおいて最終的に親化合物を遊離する生物学上活性な親化合物の化学誘導体を含む。プロドラッグは当業者によるin vivoにおける薬剤作用の発現および/または持続時間の改変を可能とし、体内での薬物の輸送、分配または溶解性を改変しうるものである。さらに、プロドラッグ製剤は毒性を減弱することも多く、あるいはまた医薬製剤を投与する場合に遭遇する問題を克服もする。プロドラッグの典型例としては、有機リン酸塩またはアルコールもしくはチオアルコールのエステルが挙げられる。Remington's Pharmaceutical Sciences, 16th Ed., A. Osol, Ed. (1980)を参照。なお、その開示は参照により本明細音に組み入れる。

[0004]

プロドラッグは親化合物または活性化合物の生物学上不活性または実質的に不活性な形態である場合が多い。活性薬物の放出速度、すなわち、加水分解速度はいくつかの要因によって、特に、親薬物と改変剤とをつなぐ結合タイプにより影響を受ける。親化合物の十分 20 な量の加水分解が起こる前に腎臓または細網内皮系などにより排出されるプロドラッグを製造することがないよう留意しなければな約ない。

[0005]

高分子をプロドラッグ系の一部として組み込むことで薬物の循環寿命が長くなることが示されている。しかしながら、約10,000ダルトン未満の1種のみまたは2種の合うをみとアルカロイド化合物などの特定の生物学上活性な物質とを複合体化した場合、特に、幾分耐加水分解性の結合が使用されている場合には、得られた複合体がin vivoで迅速に排出されることが分かっている。実際、かかる複合体は体から極めて迅速に排出されるため、加水分解が起こりやすいエステル結合が使用されている場合でさえも、治療効果に十分な親分子がin vivoにおいて再生されない。

[0006]

カンプトテシンおよび生物学上活性な関連類似体は水溶性に乏しいことが多く、PEGプロドラッグ技術によって恩恵を得る物質の例である。当技術分野でのこれまでのいくつかの研究の概要を以下に示す。

[0007]

Ohya, ら, J. Bioactive and Compatible Polymers Vol. 10 Jan., 1995, 51-66では、エステルをはじめとする種々の結合を介した2置換基の結合により作製されるドキソルビシン-PEG複合体を開示している。しかしながら、使用したPEGの分子量はせいぜい約5,000である。そのため、複合体は十分な結合の加水分解の前に実質的に排出されることから、in vivoにおける恩恵の実現は十分なものではない。

[0008]

米国特計第4、943、579号では、水溶性プロドラッグとして塩形脈の特定の単純な20(S)-カンプトテシンアミノ酸エステルを開示している。しかし、参考文献ではアルカロイドを比較的高分子量の高分子に結合させてプロドラッグを作製するための結合の一部としてアミノ酸を使用することについては開示されていない。表2で示された579人の患者に関するアータから明らかなように、加水分解は急速である。そのため、生理学的内では注入後に不溶性基剤が迅速に生じ、タンパク質と結合し、治療効果が達成される前に体から迅速に排出される。関連した取り組みは水溶性カンプトテシンナトリウム塩の開発に向けられた。[0009]

残念なことに、カンプトテシンの水溶性ナトリウム塩には依然として臨床応用に対する高 50

い有害性が残されていた(Gottlieb ら, 1970 Cancer Chemother, Rep. 54, 461; Moertel ら, 1972 上記, 56, 95; Gottlieb ら, 1972 上記, 56, 103)。

[0010]

本願出願人によるPCT公報WO96/23794では、1当量のヒドロキシル基含有薬物を高分子の各 末端に結合したビス-複合体について記載している。このような進展があったものの高分 子のペイロードをさらに高める技術が求められている。

[0011]

このように、カンプトテシンおよび関連類似体などの治療成分からなるプロドラックを作 製するさらなる技術を提供する必要性がなお存在している。本発明ではこの必要性に取り 組むものである。

【発明の開示】

[0012]

本発明の1つの態様では、式(I):

【化1】

 $R_1 = \begin{bmatrix} R_2 \\ C \\ R_3 \end{bmatrix} m \begin{bmatrix} Y_1 \\ C \\ R_4 \end{bmatrix} \begin{bmatrix} E_1 \\ C \\ E_4 \end{bmatrix} E$ 

[0 0 1 3]

(式中、

R,は高分子残基であり;

Y, do. St tunk oan:

MはO、SまたはNR、であり:

(m)は0または正の整数、好ましくは1または2であり;

(a)は0または1であり;

長は 【化2】

 $-\left(\begin{array}{c} P_7 \\ P_7 \\ P_2 \\ P_3 \end{array}\right)$ 

[0014]

であり:

E\_4は独立に、H、EIまたは

[化3]



【0015】であり:

(n)および(p)は独立に、0または正の整数であり;

Y2-3は独立に、O、SまたはNR10であり;

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R<sub>2-10</sub>は独立に、水素、C<sub>1-6</sub>アルキル、C<sub>3-12</sub>分枝鎖アルキル、C<sub>3-6</sub>シクロアルキル、C<sub>3-6</sub> 置換アルキル、C<sub>3-6</sub>置換シクロアルキル、アリール、置換アリール、アラルキル、C<sub>3-6</sub>へ テロアルキル、置換C<sub>3-6</sub>ヘテロアルキル、C<sub>3-6</sub>アルコキシ、フェノキシおよびC<sub>3-6</sub>ヘテロ アルコキシからなる群から選択され;

D、およびD、は独立に、OH、

[化4]

[0016]

または以下に示すさらなる末端分枝基である)

で表される化合物が提供される。

[0017]

式(IV)および(V)中、

(v)および(t)は独立に、0または約6までの正の整数、好ましくは約1であり;

JはNR<sub>1</sub>2または

【化5】



【0018】 であり:

L およびL, は独立に選択された二官能性リンカーであり:

Y.,,は独立に、O、SおよびNR,,からなる群から選択され;

ロアルコキシからなる群から選択され;

Arは式(I)に含まれる場合に多置換芳香族炭化水素または多置換複素環基を形成する成分であり;かつ

B,およびB,は独立に、脱離基、OH、ヒドロキシルまたはアミン基含有成分の残基からなる 群から選択される。

[0019]

本発明の1つの特に好ましい態様では、高分子残基の末端部が次の式(II): 【化 6】

(II)  $E_2 = \begin{bmatrix} E_1 & Y_1 & R_2 \\ \vdots & \vdots & \vdots \\ E_3 & E_4 \end{bmatrix}$  (II)  $\begin{bmatrix} E_1 & Y_1 & \vdots \\ \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots \end{bmatrix}$  (II)

# [0020]

(武中、

全ての置換基および変数はこれまでに定義したとおりである)

で表される成分でさらに置換されている。よって、二官能性化合物は、本明細書において B、またはB、とよばれる、2、4またはそれ以上の当量の生物学上活性な薬剤、薬物、または タンパク質が送達されうるように高分子残基(R、)がaおよび。両方の末端結合基を含有す 20 る場合に形成される。かかる二官能性高分子輸送形態の例は次の式(III):

# (化7)

 $E_{2} = \underbrace{\begin{array}{c} E_{1} \\ E_{2} \\ E_{3} \end{array}}_{E_{1}} \underbrace{\begin{array}{c} K_{2} \\ (M)_{a} \\ K_{3} \end{array} \underbrace{\begin{array}{c} K_{2} \\ (M)_{a} \\ K_{3} \end{array}}_{E_{2}} \underbrace{\begin{array}{c} E_{1} \\ (M)_{a} \\ K_{3} \\ E_{4} \end{array}}_{E_{2}} \underbrace{\begin{array}{c} E_{1} \\ E_{2} \\ E_{3} \\ E_{4} \end{array}}_{E_{2}} \underbrace{\begin{array}{c} E_{1} \\ E_{2} \\ E_{3} \\ E_{4} \\ E_{5} \\$ 

[0021]

(式中、

全ての置換基および変数は上記のとおりである)

のように示される。

[0022]

本発明の目的における「残基」とは、生物学上活性な化合物がプロドラッグ担体部分を結合するための置換反応を受けた後にも残存する生物学上活性な化合物の部分を意味するものとする。

[0023]

本発明の目的における「アルキル」とは、直鎖、分枝鎖、置換(例えば、ハロー、アルコキシー、およびニトロー) C<sub>-1</sub>アルキル、C<sub>-2</sub>シクロアルキルまたは置換シクロアルキルなどを包含するものとする。

[0024]

本発明の目的における「置換」とは、官能基または化合物に含まれる1個以上の原子に1個以上の異なる原子を付加するまたはそれと置き換えることを包含するものとする。

[0 0 2 5]

ェンなどの基を包含し; 「置換ヘテロアルキル」とは、3-メトキシ-チオフェンなどの基 を包含し; 「アルコキシ」とは、メトキシなどの基を包含し; および「フェノキシ」とは、 、3-エトロフェノキシなどの基を包含する。ハロ-はフルオロ、クロロ、ヨードおよびブ ロモを包含するものとする。

[0026]

本発明の目的における「十分な量」とは、当業者によって理解される治療効果を達成する 量を意味するものである。

[0027]

本発明の化合物の最も重要な利点の1つはプロドラックの高分子単位当たりのペイロードがこれまでの技術よりも高いことである。一般的には、高分子がまず加水分解によりトリ 10 メチルロック (TML)系プロドラッグ中間体を放出し、次いで得られた中間体または「第2のプロドラッグ」部分がラクトン化を受けて、例えば、生物学上活性な化合物またはさらなるプロドラッグを含んでなる組成物(composition)のいずれかである成分を再生することが好ましい。よって、本発明の高ペイロード高分子被合体は最大4つまでまたはそれ以上の数の薬物分子を含有しうる独自の送達系である。

【0028】 本明細書において記載する化合物および複合体の製造および使用方法も提供される。 【0029】

発明の詳細な説明

A.式 (I)

本発明の1つの好ましい実施形態では、式:

【化8】

 $R_1 = \begin{pmatrix} F_2 \\ \vdots \\ \vdots \\ \vdots \\ \vdots \\ m \end{pmatrix} \begin{pmatrix} M \\ A \end{pmatrix} = \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \begin{pmatrix} M \\ \vdots \\ M \end{pmatrix} \end{pmatrix} \begin{pmatrix}$ 

[0030]

试中、

R は高分子残基であり:

Y, dO、SまたはNR, であり:

MはO、5またはNR,であり;

(a) は0または1であり:

(m)は0または正の整数であり;

長は 【化9】

[0031]

であり;

E. ₄は独立に、H、E.または

[(k 1 0 ]

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$$- \left( \begin{matrix} \begin{matrix} R_{0} \\ C \end{matrix} \end{matrix} \right) \begin{matrix} Y_{3} \\ C \end{matrix} - D_{2}$$

[0032]

であり;

(n)および(p)は独立に、Oまたは正の整数であり;

Y,\_,は独立に、O、SまたはNR,oであり;

R<sub>-10</sub>は独立に、水素、C<sub>-6</sub>アルキル、C<sub>-1</sub>,分枝鎖アルキル、C<sub>-6</sub>シクロアルキル、C<sub>-6</sub> 置換アルキル、C<sub>-6</sub>置換シクロアルキル、アリール、置換アリール、アラルキル、C<sub>-6</sub>ヘ テロアルキル、C<sub>6</sub>をG<sub>-6</sub>ヘテロアルコキシ、フェノキシおよびC<sub>-6</sub>ヘテロアルコキシからなる群から選択され;

D,およびD,は独立に、OH、

【化11】

【0033】 (式中、 JはNR<sub>2</sub>または 【化12】

【0034】 であり;

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(v)および(t)は独立に、0または約6までの正の整数、好ましくは約1であり;

L,およびL,は独立に選択された二官能性リンカーであり; Y...,は独立に、O、SおよびNR,からなる群から選択され;

R<sub>1-17</sub>は独立に、水素、C<sub>1-6</sub>アルキル、C<sub>1-1</sub>分枝鎖アルキル、C<sub>1-6</sub>シクロアルキル、C<sub>1-6</sub>置換アルキル、C<sub>1-6</sub>では要シクロアルキル、アリール、置換アリール、アラルキル、C<sub>1-6</sub>へテロアルキル、C<sub>1-6</sub>でルコキシ、フェノキシおよびC<sub>1-6</sub>へテロアルキルを含まれた。

Arは式(I)に含まれる場合に多置換芳香族炭化水素または多置換複素環基を形成する成分であり;かつ

B,およびB,は好ましくは独立に、脱離基、OH、ヒドロキシル基含有成分またはアミン基合 10 有成分の残基からなる群から選択される) である}

で表される化合物が提供される。

[0035]

もう1つの好ましい実施形態では、D,およびD,は独立に、式(VI)

[4k 1 3 ]

(VI)

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[0036]

、中、

E, , , , , は定義内でD, およびD, が以下で定義するD', およびD', に変わることを除き、上記の E, , 4 の定義と同じ基から選択される)

で表される選択された末端分枝基である。この実施形態では、D',およびD',が独立に、OH 、式 CIV)または (V)で表される成分、または [化14]

(VII)

[0037]

(寸中、

E,,-a,は定義内でD,およびD,がD",およびD",に変わり、かつD",およびD",が独立に、OH、式(IV)または式(V)であることを除き、E,aの定義と同じ基から選択される)

で表される成分でありうる。上記のことからわかるように、末端分枝がその最大限に二官 能性高分子R、を受け入れるとすると、最大16当最の薬物が高分子プラットフォームにロー ド(Toad)できる。

[0038]

ビス-置換高分子残基が望まれるこの実施形態の態様では、本発明のいくつかの好ましい 高分子輸送系が次の式

【化15】

(III):  $E_{2} = \begin{bmatrix} E_{1} & Y_{1} & E_{2} \\ \vdots & \vdots & \vdots \\ E_{n} & E_{n} & E_{n} \end{bmatrix} \begin{bmatrix} Y_{1} & E_{1} \\ \vdots & \vdots & \vdots \\ R_{0} \end{bmatrix} \underbrace{ \begin{bmatrix} R_{2} \\ R_{0} \end{bmatrix}}_{m} \underbrace{ \begin{bmatrix} R_{2} \\ R_{0} \end{bmatrix}}_{m} \underbrace{ \begin{bmatrix} M_{1} & M_{2} \\ \vdots & \vdots \\ R_{n} \end{bmatrix}}_{m} \underbrace{ \begin{bmatrix} R_{2} \\ R_{0} \end{bmatrix}}_{m} \underbrace{ \begin{bmatrix} R_{2} \\ R_$ 

【0039】

全ての置換基および変数はこれまでに記載したとおりである)

のように示される。

[0040]

本発明のマルチ・ローディング (multi-loading)高分子輸送系は主として本明細書においてR.とよばれる高分子残基に基づくものである。所望により、R.がキャッピング基Aを含有していてもよい。高分子キャッピング基Aとしては、例えば、水素、CO.H. C.。アルキル基、およびピス系を形成する以下に示す式(II)の化合物などの成分が挙げられる: (化161

(II) 
$$E_2 = \begin{bmatrix} E_1 & Y_1 \\ \vdots & N \\ E_3 & E_4 \end{bmatrix}$$
 
$$\begin{bmatrix} R_2 \\ \vdots & R_3 \end{bmatrix}$$
 
$$\begin{bmatrix} R_2 \\ \vdots & R_3 \end{bmatrix}$$

【0041】

全ての置換基および変数はこれまでに記載したとおりである)。上記の多数の末端分枝が ビス系においても等しく適用されることが分かるであろう。

[0042]

本発明の式が含んでなるその他の置換基および変数に関しては、以下のものが好ましい: Y1.3 は各々、酸素であり;

R...o.およびR.,は各々、好ましくは水素または低級アルキル、例えば、G.。であり; R.、R.、およびR.は好ましくは-Ch.であり;

(m)は1または2であり:

(n)および(p)は各々、0または1~4の整数のいずれかであり;

(v)は0または1であり:

(t)は1であり;

L, は-(CH, CH, O), -であり; かつ

L, は-어, -, -어(어, )-、-(어, ), -, -(어, ), -NH-、-어, C(0)NHH(어, )-、-(어, ), -NH-、-C 40 H, C(0)NHH, -、-(어, ), -NH-C(0)(어, ), NH-または-어, C(0)NHH(어, 어(어, ), )-の1つであ る。

[0 0 4 3]

B.Ar成分の説明

式(I)に関して、Arは式(I)に含まれる場合に多盾換汚香族炭化水素または多盾換複素環 を形成する成分であると考えられる。重要な特徴はAr成分が本質的に芳香性であること ある。一般に、芳香族であるには、環分子面の上下にある「雲」内でπ電子が共有される 必要がある。さらに、π電子数はヒュッケル則(4n+2)に従うものでなければならない。当 乗者ならば、無数の成分がその成分の芳香族必要条件を満たし、それゆえ本発明における 使用に好適であることが分かるであろう。1つの終に好ま」い芳香族基は:

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# 【化17】

# [0044]

(式中、

R<sub>18-20</sub>はR<sub>11</sub>の定義と同じ基から選択される)

である。その他の芳香族基としては:

# 【化18】

$$R_{11}$$
 $R_{12}$ 
 $R_{13}$ 
 $R_{14}$ 
 $R_{15}$ 
 $R$ 

# [0045]

(式中、

スおよびZ,は独立に、CR2,またはNR2,であり;かつ

Z,はO、SまたはNR。1

(武中、

 $R_{1,1}$ の定義と同じ基またはシアノ、ニトロ、カルボキシル、アシル、置換アシルもしくはカルボキシアルキルから選択される)

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#### である}

が挙げられる。ペンゾおよびジベンゾ系のほか、5および6員環を有する異性体もまた包含 され、それらの関連同族体もまた包含される。また当業者ならば、ヒュッケル則に従いさ えすれば、所望により、芳香環がO、S、NR,,などのヘテロ原子で置き換えられてもよいこ とが分かるであろう。さらに、所望により、芳香族または複素環式構造が当技術分野で一 般的に理解されているハロゲンおよび/または側鎖で置き換えられてもよい。また、本発 明のAr成分に好適な全ての構造はB、またはB、含有基および(R、)基を同一平面のオルト位 に存在させることが可能である。

## [0046]

## C.プロドラッグの加水分解による薬物生成

本発明のプロドラッグ化合物は、血漿中の加水分解も、ノ。が排出も、ノ。よりも短くなるように ように設計される。

#### [0 0 4 7]

治療を受けている哺乳類の血漿中における本発明の化合物に含まれる結合の加水分解しい。 は、排出前に、十分な量の親化合物(すなわち、アミノまたはヒドロキシル基含有生物活 性化合物)を放出させるのに十分短い加水分解ちょである。本発明のいくつかの好ましい 化合物の血漿中における加水分解のも、は約5分~約12時間の範囲である。好ましくは、 組成物の血漿加水分解も、が約0.5~約8時間の範囲、さらに最も好ましくは約1~約6時間 の範囲である。

#### [0 0 4 8]

#### D.実質的に非抗原性である高分子

上記のように、R、はポリアルキレンオキシド(PAO)またはポリエチレングリコール(PEG)な どの好ましくは実質的に非抗原性である水溶性高分子残基である。本発明の好ましい態様 では、R.は本明細費においてAとよばれる、二官能性またはビス-高分子系を形成しうる上 記のキャッピング基をさらに含む。

#### [0.049]

例として、本発明の組成物のPEG残基部分は、限定されるものではないが、次の:

-C(=Y, )-(CH, ), -O-(CH, CH, O), -A,

-C(=Y, )-Y, -(CH, ), -0-(CH, CH, O), -A.

-C(=Y, )-NR,, -(CH, ), -O-(CH, CH, O), -A,

-(CR, AR, , ), -0-(CH, ), -0-(CH, CH, O), -A,

-NR, , -(CH, ), -0-(CH, CH, O), -A.

-C(=Y, )-(CH, ), -O-(CH, CH, O), -(CH, ), -C(=Y, )-,

-C(=Y, )-Y, -(CH, ), -0-(CH, CH, O), -(CH, ), -Y, -C(=Y, )-,

-C(=Y<sub>6</sub>)-NR, , -(CH, ), -O-(CH, CH, O), -(CH, ), -NR, , -C(=Y<sub>6</sub>)-,

-(CR, 4R, 6), -0-(CH, CH, O), -(CH, O), -0-(CR, 4R, 6), -, \$\dagger \dagger \text{\$\dagger } \text{\$\dagger

-NR, , -(CH, ), -0-(CH, CH, O), -(CH, ), -NR, , -

(式中、

Y<sub>6</sub>およびY<sub>7</sub>は独立に、O、SまたはNR<sub>2</sub>3であり;

#### xは重合度であり;

Ra,、Ra,およびRa,は独立に、H、Ca,アルキル、Ca,a分枝鎖アルキル、Ca,aシクロアル キル、C<sub>1-6</sub>置換アルキル、C<sub>3-8</sub>置換シクロアルキル、アリール、置換アリール、アラルキ ル、Ҁ.。ヘテロアルキル、置換Ҁ.。ヘテロアルキル、Ҁ.。アルコキシ、フェノキシおよび C. ヘテロアルコキシからなる群から選択され:

eおよびfは独立に、0、1、または2であり; かつ

Aはキャッピング基である)

から選択されうる。

#### [0050]

高分子の重合度(x)は約10~約2,300でありうる。これは高分子鎖の繰り返し単位数を示す ものであり、高分子の分子量に依存している。(A)部分は本明細書において記載するキャ

ッピング基、すなわち、高分子の末端に見られる基であり、いくつかの態様では、H、NH、 、OH、COH、C、アルキルまたは当業者によって理解されているその他のPEG末端活性化 基のいずれかから選択されうる。

[0051]

また、ポリプロピレングリコール、本願出願人による米国特許第5,643,575号で記載されたものなどの分枝PEG誘導体、Shearwater Polymers、Inc. カタログ "Polyethylene Glyc ol Derivatives 1997-1998"で記載されたものなどの「是型PEG」および分岐したPEGも有用である。なお、上記の各々の開示は参照により本明細書に組み入れる。要すれば、過度の試験を行うことなく、二官能性結合基との結合のために水溶性高分子を官能化しうることが分かるであろう。

[0052]

さらなる実施形態では、R.は所望により、1種以上のデキストラン、ポリビニルアルコール、炭水化物系高分子、ヒドロキシブロビルメタクリルアミド、ポリアルキレンオキシドおよび/またはそのコポリマーから選択されてもよい。本願出願人による米国特許第6,153,655号も参照されたい。なお、その内容は参照により本明細書に組み入れる。

[0053]

本発明の多くの態様では、複数置換高分子複合体が望まれる場合にはビス-活性化ポリエ チレングリコールが好ましい。また、一置換高分子が望まれる場合にはポリエチレングリ コール(PEG)、モノメチル基を末端にもつポリエチレングリコール(mPEG)などのモノ活性 化C<sub>--</sub>アルキル基を末端にもつポリアルキレンオキシド(PAO)が好ましい。

[0 0 5 4 ]

所望の加水分解可能な結合を提供するためには、モノまたはジPECアミンおよびモノまたはジPEGフォールのほか、PEG酸またはPEG二酸などの一または二酸活性化高分子も使用できる。好適なPAO酸はまずmPEG-OIやエチルエステルに変換し、その後、酸化することにより合成できる。Gehrhardt, H., 6、Polymer Bulletin 18: 487 (1987)およびVeronese, F. M., 6, J. Controlled Release 10; 145 (1989)も参照されたい。また、PAO酸はmPEG-OHをエプチルエステルに変換し、その後、酸関裂することにより合成できる。例えば、本郷出願人による米国特許第5,605,976号を参照されたい。なお、上記の各々の開示は参照により本明細書に組み入れる。

[0055]

PAOおよびPEGは平均分子量の点で実質的に異なりうるが、本発明のほとんどの態様においてプロドラッグの高分子部分の重量平均分子量は少なくとも約20,000である。好ましくは、R.の重量平均分子量は約20,000~約100,000、さらにより好ましくは約25,000~約60,000である。プロドラッグに合有させるのに選択される高分子の平均分子量は、リンカーの加水分解前に、プロドラッグの十分な循環を提供するのに十分なものでなければならない

[0056]

本明細書において包含される高分子物質は、好ましくは室温で水溶性である。限定されるものではないが、かかる高分子としては、ポリエチレングリコール(PEO)またはポリプロピレングリコールなどのポリアルキレンオキシドホモポリマー、ポリオキシエチレン化ポ 40 リオール、およびそのコポリマー、ならびにブロックコポリマーの水溶性が維持される場合にはそのブロックコポリマーが挙げられる。

[0057]

PECなどのPAOについて本明細書において記載したように同様の活性化が行われるなら、デキストラン、ポリビニルアルコール、炭水化物系高分子、ヒドロキンプロビルメタクリルアミド(HPMA) あよびそのコポリマーなどのような有効に非抗原性な材料をPAO系高分子の代わりとして使用できる。当業者ならば、上記のリストは例示にすぎず、本明細書において記載する性質を有する全ての高分子材料が包含されることが分かるであろう。本発明の目的では、「有効に非抗原性」および「実質的に非抗原性」とは、当技術分野において実質的に毒性がなく、かつ哺乳類において感知できる免疫応答を誘導しないと認識される50

全ての高分子材料を包含するものと理解される。

- [0058]
- ポリプロピレングリコール酸など上記のもの以外のポリアルキレンオキシド誘導体、ならびにその他の二官能性結合基もまた包含されることは上記の説明から明らかであろう。
- [0059]
- E.プロドラッグ候補
- 1. <u>ヒドロキシル基含有化合物の残基</u> a. カンプトテシンおよび関連トポイソメラーゼI阻害剤

カンプトテシンは中国で自生するカンプトテカ・アクミナタ (Camptotheca accuminata)の 樹木およびインドで自生するカサミズキ (Nothapodytes foetida)の樹木で産生される水に 10 不溶性の細胞傷害性アルカロイドである。カンプトテシンおよび関連化合物ならびに類似 体は有望な抗癌または抗腫瘍剤であることも知られており、さらにこれらの活性がin vit roおよびin vivoにおいて発揮されることも分かっている。また、カンプトテシンおよび 関連化合物は本発明のプロドラッグへの変換候補でもある。

[0060]

カンプトテシンおよび特定関連類似体は共通した構造:

# 【化19】

In 2014 1/2

【0061】 を有している。

#### [0062]

この主要構造から、いくつかの公知な類似体が製造されてきた。例えば、A環はOHで10.38 よび11位のいずれかまたはその両方を置換しうる。また、A環は直鎖または分枝鎖C\_3。ア かキルまたはC\_3、アルコキシ(所望により、ヘテロ原子、すなわち、Oまたはで環と結合していてもよい)で9位も置換しうる。B環は直鎖もしくは分枝鎖C\_3。アルキルもしくは置換アルキル、C\_3シクロアルキル、C\_3・2・アルコキシ、ア・アルコ・アル・アルキルなど、アルキルル、アシカロアルキル、C、3・アルコキシ、フェニルアルキルなど、アルキルル、アラルキルなどで7位を置換しうる。C、DおよびE環でもその他の置換が可能である。内含は参照により本明細書に組み入れる。かかる誘導体は一般であるが表現である。本発明における使用に好きしいカンプトテシン誘導体としては、20-04または本明細書に組み入れる。かかる誘導体は過度な試験を行わなくとも、公知の合成方法を用いて作製できる。本発明における使用に好ましいカンプトテシン誘導体としては、20-04または本明細書に組み入れる。かかる誘導体は過度な試験を行わなくとも、公知の合成方法を用いて作製できる。本発明における使用に好ましいカンプトテシン誘導体としては、20-04またはつの63年と結合する結合部分中間体、例えば、イミノ二酢酸などと 40 反応しらるもう1つの04基を含むものが挙げられる。本明細書において記載したカンプトテシン類似なは例示を目的とするものであって、これに限定されない。

#### [0063]

# b. タキサン系化合物およびパクリタキセル誘導体

本発明のプロドラッグ組成物に含められる化合物種の1つがタキサン系化合物である。本発明の目的では、「タキサン」とは、タキサン系テルベンに入る全ての化合物を包含するものである。よって、タキソールCパクリタキセル)、3-電換 tert-ブトキシーカルボニルーアミン誘導体(タキソテール)など、ならびに標準有機技術を用いて容易に合成されるまたはSt. Louis, MissouriのSigma Chemicalなどの民間供給会社から入手可能であるその他の類似体は本発明の範囲である。これらの誘導体は有効な抗癌剤であることが5分かって 50

いる。多くの研究により、これらの薬剤が数種類の悪性腫瘍に対する活性を有することが 示されている。現在まで、それらの使用には、特に、それらの供給が不足しており、水溶 性が乏しく、さらに過敏症を引き起こす傾向があることから厳しい制限があった。本願出 願人による米国特許第5,622,986号および第5,547,981号で開示された7-アリール-カルバ メートおよび7-カルバザートをはじめとするその他のタキサン系化合物もまた本発明のプ ロドラッグに含めうることは理解すべきである。なお、上記米国特許の内容は参照により 本明細書に組み入れる。パクリタキセルは好ましいタキサンである。

#### [0064]

# c.さらなる生物活性成分

上記分子のほか多くの化合物を用いて本発明のプロドラッグ製剤が製造できる。例えば、 10 ビス-PEG複合体などの生物学上活性な化合物が、 ゲムシタビン:

## [1] 2 0 ]

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# [0066]

または

フルコナゾールなどのトリアゾール系抗真菌薬:

an

[化23]

[0068]

または Ara-C: 【化24】

HO OH

[0069]

などの化合物から誘導された。

#### [0070]

本発明の高分子系プロドラッグは特にかかる水不溶性化合物を送達するのに十分に好適なものであるが、プロドラッグ形態用に選択される親化合物が実質的に水不溶性である必要はない。その他の有用を親化合物としては、例えば、生物学上活性な特定の低分子量タンパク質、酵素およびペプチドグリカンをはじめとするペプチド、ならびにその他の抗腫瘍剤:フォルスコリンなどの心血管作動薬:コンプレタスタチン、ピンプラスチン、ドキソ 50 ルビシン、メイタンシなどの抗血管作動薬:コンプレタスタチン、ピンプラスチン、ドキソ 50 ルビシン、メイタンシなどの抗難に動き、アンコマイシン、エリスロマイシンなどの抗感感染症薬;ナイスタチン、アムホテリシンB、トリアゾール、パピュロキャンディン、ニューモキャンディン、エナキャンディン、ポリオキシン、ニュローマイシ、プラジミシン、ペナノミシンなどの抗夷菌薬("Antibiotics That Inhibit Fungal Cell Wall Development" Annu. Rev. Microbiol. 1994, 48: 471-97(その内容は参照により本明細書に組み入れる)を参照されたい):抗不安薬、胃腸薬、中枢神経系活性化剤、鎮痛剤や排卵態発剤または選妊薬、抗炎症薬、ステロイド系薬剤、抗尿酸血症薬、心血管作動剤に血管拡張薬、血管収縮薬などが挙げられる。

#### [0071]

上記のものは本発明のプロドラッグに好適である生物学上活性な成分の例示である。特記 40 していないが、好適なエステル形成基、すなわち、ヒドロキシル基を有する生物学上活性な材料もまた本発明の範囲とされるものと理解すべきである。また、本発明のプロドラッグ複合体が、1当量の薬物および高分子だけでなくin vivoにおいて生物活性に影響を及ぼさない成分を含有する少量の化合物も含有してよいことも理解すべきである。例えば、いくつかの例では、二酸と 1 個の結合ポイントを有する薬物分子とを反応させても、その反応条件では高分子当たり2当量の薬物を有するプロドラッグが定量的な量で生成されないということが分かっている。カルボジイミドを使用する場合にはアシル尿素などの反応副生成物が生じる場合がある。

[0072]

2. アミン基含有化合物の残基

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本発明のいくつかの態様では、B、またはB、はアミン基合有化合物の残基である。限定されるものではないが、かかる好適な化合物としては、有機化合物、酵素、タンパク質、ポリベブチドなどの残基が挙げられる。有機化合物としては、関定されるものではないが、ダウノルビシン、ドキソルビシン、Pーアミノアニリンマスタード、メルファラン、Ara-C(シトシンアラビノシド)などをはじめとするアントラサイクリン系化合物、および関連代謝
拮抗性化合物、例えば、ゲムシタビン、などの成分が挙げられる。あるいは、Bはアミン基合有心血管作動剤、抗新生物薬、抗感染症薬、ナイスタチンおよびアムホテリシンBなどの抗真菌薬、抗不安薬、胃腸薬、中枢神経系活性化剤、鎮痛薬、排卵誘発剤、避妊薬、抗炎症薬、ステロイド系薬剤、抗尿酸血症薬、血管拡張薬、血管収縮薬などの残基でありる。

[0073]

本発明の好ましい態様では、アミノ基含有化合物は、動物、例えば、ヒトをはじめとする 哺乳類のかかる治療が望まれる症状の治療における医薬上のまたは診断上の使用に好適な 、生物学上活性な化合物である。上記のものは例示を意図するものであり、改変しうる化 合物を限定するものではない。当業者ならば、その他のかかる化合物も過度な試験を行う ことなく同様に変変しうることが分かるであるう。特に示していないが、好適なアミノ基 を有する生物学上活性な材料もまた本発明の範囲とされるのと理解すべきである。

[0074]

本発明において含有させるのに好適なアミノ基含有分子のタイプについての唯一の条件は、担体部分と反応しかつそれと結合しうる利用可能な少なくとも1つの(第1または第2)アミン基含有位置が存在することと、プロドラッグ系が親化合物を放出して、親化合物を再生利用した後に生物活性の実質的な喪失がないことである。

[0075]

本発明のプロドラッグ組成物への含有に好適な親化合物は、それ自体が結合超組成物から の加水分解による放出後は活性ではないが、さらなる化学工程/反応を受けた後に活性と なりうる物質/化合物であってよいことに注目されたい。例えば、ダブルプロドラッグ輸 送系によって血流に送達される抗癌剤は、癌または腫瘍細胞に浸透するまで不活性な状態 にあり、そこで癌または腫瘍細胞化学、例えば、その細胞に特異的な酵素反応により活性 化されると考えられる。

[0076]

3.脱離基

B、またはB、が脱離基である態様では、好適な脱離基としては、限定されるものではないが、N-ヒドロキシベンプトリアゾリル、ハロゲン、N-ヒドロキシフタルイミジル、p-ニトロフェノキシ、イミダゾリル、N-ヒドロキシスクシンイミジル;チアゾリジニルチオンなどの基を挙げることができ、あるいは当業者には理解されるその他の好適な脱離基が挙げられる。本明細書において使用し記載する合成反応は過度の試験を行わなくとも当業者ならば分かるであろう。

[0077]

例えば、化合物(I)のアシル化中間体をクロロ蟻酸4-ニトロフェニル、ジスクシンイミジルカーボネート(OSC)、カルボニルジイミダゾール、チアゾリジンチオンなどの反応物質と反応させて所望の活性化誘導体を得ることができる。

[0078]

p-とドロキシベンジルアルコールまたはp-アミノベンジルアルコール、およびo-ヒドロキシベンジルアルコールまたはo-アミノベンジルアルコールのフェノールまたはアニリン部分の選択的アシル化は、例えば、チアゾリジンチオン活性化高分子、スクシンイミジルカーボネート活性化高分子、カルボン酸活性化高分子、プロックアミノ酸誘導体を用いて行うことができる。適切に実施されれば「活性化」型PECプロドラッグ(またはプロックプロドラッグ)はフェンまたはヒドロキシル基合有化合物との複合体化が可能である。

[0079]

F.高分子プロドラッグ輸送系の合成

典型的な高分子プロドラッグの合成を実施例で記載するが、一般に、プロドラッグ輸送系を製造する1つの好ましい方法では、最初に高分子残基を分枝基に結合させる。別途、生物学上活性な成分または薬物、例えば、薬物-OHまたは薬物-NH、(氏1のB、またはB、)をTML 成分に結合させる。このTM 成分は、高分子との結合ポイントに二官能性スペーサーを含んでもよい。次に、末端分枝を有する高分子残基と薬物-TML成分とを最終生成物を生成するのに十分な条件下で反応させる。

#### [0080]

二官能性スペーサーを含有するTML-薬物成分と高分子部分との結合は、好ましくはカップリング剤の存在下で行われる。 限定されるものではないが、好適なカップリング剤としては、例えば、Sigma-Aldrich Chemicalなどの民間供給会社から入手可能である、またはな 10 知の方法により合成される1,3-ジイソプロピルカルボジイミド(DIPC)、好適なジアルキルカルボジイミド、ハロゲン化2-ハロ-1-アルキルーピリジニウム、(Mukaiyama試薬)、1-(3-ジメチルアミノプロピル)-3-エチルカルボジイミド(BDC)、プロパンホスホン酸環状無水物(PPACA)およびジクロロリン酸フェニルなどが挙げられる

#### [0081]

好ましくは、置換基を塩化メチレン、クロロホルム、DMFまたはその混合物などの不活性 溶媒中で反応させる。この反応は、好ましくは生成した全ての酸を中和するためにジメチ ルアミノビリジン、ジイソプロビルエチルアミン、ピリジン、トリエチルアミンなどの塩 基の存在下、0℃~約22℃(容温)の温度で行われる。

# [0082]

より詳細には、高分子輸送系を製造する1つの方法は式(VIII): 【化 2.5.】

#### [0083]

(式中、

全ての置換基および変数はこれまでに定義したとおりであり、かつ B', はヒドロキシルまたはアミン基含有成分の残基である)

で表される化合物と式(IX):

(IX)  $R_1 \longrightarrow \begin{pmatrix} R_2 \\ C \end{pmatrix} \longrightarrow \begin{pmatrix} M \end{pmatrix}_a C$ 

[0084]

(式中.

R,は高分子残基であり;

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YidO、SまたはNR。であり、

MはO、SまたはNR、であり: (a)は0または1であり;

(m)は0または正の整数であり:

Y2-, は独立に、O、SまたはNR, であり;かつ

R<sub>2-3</sub>は独立に、水素、C<sub>1-6</sub>アルキル、C<sub>3-12</sub>分枝鎖アルキル、C<sub>3-8</sub>シクロアルキル、C<sub>1-6</sub> 置換アルキル、C3-8置換シクロアルキル、アリール、置換アリール、アラルキル、C1-6へ テロアルキル、置換C.-6ヘテロアルキル、C.-6アルコキシ、フェノキシおよびC.-6ヘテロ アルコキシからなる群から選択され:

足は

[1]: 27]



[0085]

であり;

East独立に、H、Estたは

【化28】



[0086]

(式中、

D、およびD、は独立に、OHまたは保護されていないアミンまたはヒドロキシルと反応しうる 脱離基、または末端分枝基であり:

(n)および(p)は独立に、Oまたは正の整数であり;

Y2-, は独立に、O、SまたはNR, であり;かつ

 $R_{s-10}$  は独立に、水素、 $C_{s-6}$  アルキル、 $C_{s-12}$  分枝鎖アルキル、 $C_{s-8}$  シクロアルキル、 $C_{s-6}$ 置換アルキル、C3-6 置換シクロアルキル、アリール、置換アリール、アラルキル、C3-6へ テロアルキル、置換C\_。ヘテロアルキル、C\_。アルコキシ、フェノキシおよびC\_。ヘテロ アルコキシからなる群から選択される)

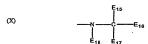
である~

で表される化合物とを反応させることを含む。

[0087]

この方法のさらなる態様では、D,およびD,は独立に、式(X)

【化29】



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[0088]

(式中、

E, , \_ , , はD, およびD, が以下で定義するD', およびD', に変わることを除き、E, \_ , の定義と同じ基から選択される)

で表される選択された末端分枝基である。この実施形態では、D',およびD',が独立に、OH、式(IV)または(V)で表される成分、または(XI)

【化30】



. [0089]

(式中、 E,,,,,はD,およびD,がD',およびD'',に変わり、かつD'',およびD'',が独立に、OH、または保 渡されていないアミンもしくはヒドロキシルと反応しうる脱離基と定義されることを除き 、E,-,の定義と同じ基から選択される)

で表される成分でありうる。

[0090]

かかる合成方法により、最大16当量のカルボン酸または活性化カルボン酸を、例えば、結合させることが可能である。本明細書における好ましい構造で示されるように、末端分枝多酸を有するPEG残基が本発明の好ましい態様である。

[0091]

選択された合成方法にかかわらず、本明細書において記載する合成方法によって得られる 好ましい化合物としては、

【化31】

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【0092】 および 【化32】

【0093】 (式中、

R はPAOまたはPEGなどの高分子残基であり、かつDはOH、式(IV)または(V)である。好まし 20 くは、Dは [化33]

【0094】 または 【化34】

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[0095]

**(** 大中、

Bはアミンまたはヒドロキシル基含有薬物の残基である)

である}

が挙げられる。

[0096]

本発明のもう1つの好ましい態様では、本発明の化合物は式(XII): 【化35】

# [0097]

(式中、

全ての置換基および変数はこれまでに定義したとおりである)

で表される。

[0098]

G.in vivo診断学

本発明のさらなる態様は、所望により、診断または造影目的に選択される診断タグを上記の輸送エンハンサーに付けて作製してもよい本発明の複合体を提供する。そのため、好適なタグは、好適な成分、例えば、アミノ酸残基を、当技術分野の標準放射性同位元素、放射線不透過性標識、磁気共鳴機能、またはその他、磁気共鳴映像法に好適なその他の非放射性同位元素機能、蛍光機識、外科処置中の腫瘍組織のイメージングを可能にする可視色を呈する標識および/または紫外線、赤外線または電気/をで並光発光元能な標識などに結合させることにより作製される。所望により、診断タグを複合体化される治療成分に組み込みおよび/または結合させて、動物またはヒト患者内での治療用生物活性材料の分布のモニクリングを可能にすることができる。

[0099]

本発明のなおさらなる態様では、本発明のタグ付き複合体が当技術分野で公知な方法により、例えば、放射性同位元素標識をはじめとする好適な標識を用いて容易に作製される。一例として、これらにはin vivoにおいて腫瘍細胞に選択的に取り込まれる放射免疫シンチグラフ用薬剤を製造するための<sup>131</sup> ヨウ素 <sup>137</sup> ヨウ素 <sup>378</sup> テクネチウムおよび/または<sup>111</sup> インジウムが挙げられる。例えば、一例として、参照により本明細書に組み入れる米国特許第5,328,679号;同第5,888,474号;同第5,997,844号;および同第5,997,845号により示されたものをはじめとする、ペプチドをTc-99mに結合させる当技術分野で公知な方法が多数ある。

[0100]

一般には、患者の腫瘍組織の解剖学的位置決定では、腫瘍を有することが予測される患者 または動物に複合体タグを投与する。標準化免疫グロブリンを腫瘍部位に位置付けるのに 十分な時間が経過した後、標準により発生するシグナルを、例えば、X線ラジオグラフィ 、コンピュータ体軸横断X線断層撮影、MRIにより、発光性タグの機器検出により、ガン マカメラなどのフォトスキャン装置、または選択されたタグの性質に好適なその他の方法 もしくは装置により視覚的に検出する。

[0101]

次いで、検出されたシグナルを画像または腫瘍部位の解剖学的および/もしくは生理学的 判定に変換する。この画像によりin vivoにおける腫瘍の位置付けが可能になり、好適な 治療計画の立案ができる。タグ付き成分自体が治療薬である実施形態では、検出されたシ <sup>20</sup> グナルによって治療中の解剖学的位置決定が明らかであり、診断的および治療的インター ベンションを追跡するための基準が提供される。

[0102]

H.治療方法

本発明のもう1つの態様により、哺乳類における種々の病状に向けた治療方法が提供され これらの方法は、かかる病状の治療が必要な哺乳類に、有効量の、本明細書において 記載するように製造したマルチ・ローディッド(multi-loaded)Ara-C-PEC複合体などのブ ロドラッグを投与することを含む。該組成物は特に、新生物性疾患を治療する、全身腫瘍 組織量を減少させる、新生物転移を予防する、および哺乳類における腫瘍/新生物増殖の 再発を予防するのに有用である。

[0103]

投与するプロドラック量はその中に含まれる親分子に応じたものとなる。一般に、治療方法に使用するプロドラック量は哺乳類において所認の治療効果を効果的に達成する量である。必然的に、種々のプロドラッグ化合物の投与量は親化合物、in vivo加水分解速度、高分子の分子量などによっても多少変わるが、一般には、タキサン系プロドラッグはタキサン部分の量を基に1日当たり約5~約500mg/mf の範囲の量で投与される。また、カンプラシンプロドラッグも1日当たり約5~約500mg/mf の範囲の量で投与される。また、カンプ定に列示であり、廊床経験および治療適用に基づき、選択されたプロドラッグの最適投与量が当業者により決定されるであろう。実際の投与量については必要以上の試験を行うことなく、当業者には明らかであろう。

[0104]

哺乳類へ投与するために本発明のプロドラッグを1種以上の好適な医薬組成物に含めることができる。医薬組成物は当技術分野で十分に公知な方法に従って製造される液剤、懸濁 別、錠剤、カプセル剤などの形態であってよい。また、当業者が要すれば、かかる組成物の 校与は経口および/または非経口経路によるものであってよいと考えられる。組成物の ・ 格波はび/または懸濁液は、例えば、当技術分野で公知な方法、例えば、静脈内、筋内 の、皮下片針などによる組成物のドネスまなは骨側用の相体ビヒクルドして使用し、うる。

[0105]

また、かかる投与は体内スペースもしくは体腔への注入、ならびに吸入および/または経 鼻経路によるものであってもよい。しかしながら、本発明の好ましい態様では、プロドラ 50

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ッグはその必要のある哺乳類に非経口投与される。

【実施例】

[0106]

# 1.実施例

次の実施例は本発明をさらに理解するためのものであり、本発明の有効な範囲を何ら制限 するものではない。実施例で列挙される下線を施した太字体の数字は図1~5で示されるも のと対応している。

[0107]

#### 概説

反応は全て乾燥窒素またはアルゴン雰囲気下で行った。市販の試薬はさらなる精製を行わ 10 ずに使用した。全てのPEC化合物は使用前に真空下または共沸蒸留(トルエン)により乾燥させた。 \*Hスペクトルは特に断りのない限り、溶媒としてジュウテリオクロロホルムを用いてJEOL FT NMF システム JNM GSX-270装置で測定した。 \*1°C NMRスペクトルはJNM GSX-270装置で測定した。 \*1°C NMRスペクトルはJNM GSX-270装置で測定した。 \*1°D NMRスペクトルはJNM GSX-270装置で測定した。 \*1°D NMRスペクトルはJNM GSX-270では67、80M化で測定した。 化学シフト(c) 以チトラメチルシラン CTNS)から低速へ向かう百万分の一(ppm)単位で表され、結合定数(J値)はヘルツ(セ2)で示される。 in vivo薬物処理前の注入日に全てのPEC複合体化化合物を減度建攻(0.9%)に溶解し(~15mg/m L)、それらをara-C等価物として投与した(絶対量のara-Cを投与)。

# [0108]

# HPLC法

G3逆相カラム (Beckman, ultrasphere)を用い、移動相としてメタノールー水の80:20混合物 20 (V/V)を用いる 定組成条件下でHPLC分析を行った。ビーク溶出は案外吸光検出器を用いて2 S4mmでモニターした。 遊離PECの存在を検出し、さらにPEC化生成物の存在も確認するため、蒸発光散乱検出器 (ELSD)、PL-EMO 950型 (Polymer Laboratories)を使用した。ELSDおよびUV分析では、全ての最終PEC化生成物には非改変薬物が含まれず、HPLCによる純度は≥9 S%であった。

[0109]

#### PEG誘導体中のAra-C含量の分析

[0110]

## PEG誘導体中のメルファラン含量の分析

[0111]

#### 略語

DOM(ジクロロメタン)、DMAP(4-(ジメチルアミノ)ピリジン)、EDC(1-エチル-3-(3-ジメチルアミノブロピル)カルボジイミド)、HOBT(1-ヒドロキシベンブトリアゾール)、IPA(2-ブロバノール)、MM(N-メチルモルホリン)、TRA(トリフルオロ酢酸)。

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## [0112]

# [実施例1] <u>化合物3a</u>

無水ビリジン(50mL)中のara-C(1, 1.73g, 7.12mmol), 2a(700mg, 1.78mmol), HOBT(0.96g 7.12mmol))。 およびEDC・HC1(2.73g, 14.25mmol))の混合物を室温で2時間機拌し、温度を40℃に上昇させてこの反応を一晩続けた。 音媒を除去し、塩化メチレン(50mL)を用いて混合物を溶解した後、水(3×30mL)、次ぎに、0.1M HC1(2×30mL)で洗浄した。 有機層を無水M550、で乾燥させ、溶媒を実空除去すると粗生成物が得られた。これをシリカゲルカラムクロマトグラフィー(DOM中5~100%HC0H)により精製し、638.8mg(52%)の3aを白色の固体として得た: H NMR & 1.42, 1.55, 2.17, 2.26, 2.46, 2.79, 3.84, 3.91, 4.14, 4.33, 4.53, 5.49, 6.07, 6.17, 6.52, 6.76, 7.31, 7.67, 8.16, 8.62; 10.7 NMR & 1.77, 20.11 10, 25.36, 28.32, 31.51, 31.96, 39.57, 50.18, 50.45, 61.88, 74.50, 80.15, 85.90, 88.58, 96.25, 122.51, 132.82, 133.34, 136.73, 138.22, 146.57, 149.90, 155.65, 155.96, 162.08, 171.89, 174.06,

# [0113]

# [実施例2] <u>化合物3b</u>

化合物1を実施例1と同様の条件を用いて2bと結合させ、3bを54%の収率で得た:<sup>13</sup>C NMR & 17.23, 17.92, 18.33, 25.49, 28.32, 31.51, 31.58, 31.99, 32.46, 39.52, 40.09, 50.8, 50.22, 61.72, 74.50, 74.94, 80.11, 80.15, 85.45, 85.90, 88.01, 88.58, 96.25, 122.51, 128.77, 129.03, 129.16, 131.68, 132.82, 136.24, 136.73, 138.22, 146.05, 146.57, 149.90, 155.65, 155.96, 171.85, 171.89, 174.06, [0 1 1 4 ]

# [実施例3] 化合物4a

# [0115]

### [実施例4] 化合物4b

化合物 3b を実施例3と同じ条件に付し、4b を 82%の 収率で得た: 'H NMR (DMSO-d\_) & \_1.52 (s, 3H, (CH\_), CH) 1.55 (s, 3H, (CH\_), CH), 1.62 (d, 1 H, 1 = 8.1 Hz, (CH\_), CH), 2.22 (s, 3H, CH\_, Ar), 2.57 (s, 3H, CH\_, Ar), 2.97 (s, 2H, CH\_, C(=0)), 3.41—4.27 (m, 5 H, ara—C's H-2'+H5'), 6.09 (d, 1H, J = 5.4, ara—C's H-1'), 6.67 (s, 1H, Ar-H), 6.90 (s, 1H, Ar-H), 7.12 (d, J = 5.4, H-6), 8.05 (d, 1 = 8.1, H-5), 8.67 (b, 5.1H, TFA); 13 C NMR (DMSO-d\_) & \_15.4, H-6), 8.05 (d, 1 = 8.1, H-5), 8.67 (b, 5.1H, TFA); 13 C NMR (DMSO-d\_) & \_15.4, H-6), 8.05 (d, 1 = 8.1, H-5), 8.67 (b, 4.1, 48.53 4, 4.9.0, 61.02, 64.94, 74.64, 76.14, 85.74, 86.95, 94.32, 122.32, 132.41, 134.08, 135.67, 138.09, 146.71, 149.20, 154.50, 158.21, 158.72, 162.02, 169.68, 171.87

# [0116]

## 「実施例5] 化合物6a

無水DM(50mL)中のPEG-アスパラギン酸(分子量40,000,5,3 g,0.074mmol)、4a(385.6mg,0.74mmol)、MM(240mg,2.38mmol)、HDBT(120.5mg,0.89mmol)、およびEDC・HCI(228.4 mg,1.19mmol)の混合物を0℃で30分間攪拌した。この反応物を室温に湿め、反応を3日間続け、濾過した。連液を真空濃縮し、残渣をIPAで再結晶化させ、2.7g(90%)の生成物を得た。UVアッセイで測定した生成物中のara-C量は2.11重星%であった:<sup>13</sup>C MMR g 14.40,1 50

9.22, 24.86, 31.17, 38.26, 38.90, 47.94, 48.67, 49.66, 60.17, 61.12, 61.90, 67.8 6-70.87 (PEO), 71.70, 74.50, 85.01, 87.53, 95.28, 121.39, 131.18, 132.68, 133.19, 134.77, 137.70, 145.26, 138.93, 155.23, 160.12, 161.56, 168.39, 170.72, 170.92, 171.27, 171.34,

# [0117]

[実施例6] 化合物6b

化合物4bを実施例5と同じ条件に付し、6bを88%の収率で得た。UVアッセイで測定した生成物中のara-C量は1.68重量%であった;<sup>33</sup> C NMR<sub>6</sub> 15.12, 16.22, 24.52, 24.73, 29.55, 30.55, 31.15, 38.04, 38.59, 47.66, 49.16, 49.93, 50.18, 60.93, 61.12, 62.90, 69.44 -71.59 (PEG), 71.70, 74.50, 84.78, 84.90, 87.53, 94.85, 127.60, 130.20, 135.51, 10.136.10, 141.70, 145.15, 147.50, 155.00, 161.20, 169.47, 170.62, 170.92, 171.27。

# [0118]

「実施例7」 化合物9

PEGジオール(7,55g, 1.38mmol)を2時間トルエンと共沸させた後、回転蒸発により200mLの溶媒を除去した。この溶液を~30℃に冷却し、トリホスゲン(0.544g, 1.83mmol)を固体とて、次ぎに、無水ビリジン(0.434g, 5.49mmol)を加え、反応混合物を50℃で1時間境 搾した。トセドロキシフタルイミド(8,1.12g,6.88mmol)および無水ビリジン(0.54g,6.88mmol)をクロロ蟻酸混合物に加え、反応物を50℃でさらに2時間、次ぎに、室温で12時間 機拌した。この反応混合物を濾紙で濾過し、溶媒を実空除去し、生成物を塩化メチレン-エチルエーテル(1100mL,8:2, v/v)で再結晶化させ、生成物を得た(50.9g,92%:<sup>13</sup>C NMR 20 & 123.62,128.10,134.55,152.00,160.00。

# [0119]

「実施例8] PEG-cmc-Asp-O-t-Bu(11)

化合物9(分子量40,000, 20g, 0.459mmo1)およびアスパラギン酸ジt-ブチルエステルHC1(1 0, 1.0g, 3.55mmo1)を無水DCMに溶解した後、DMAP(0.433g, 3.55mmo1)を加えた。この溶液を一晩還流した後、エチルエーテル(11)を加えて沈酸させた。濾過により固体を単離し、IFACLL)で2回再結晶化させた。濾過ケーキをIFA(200m1)およびエーテル(200m1)で洗浄し、45℃で真空乾燥させた後に15.6g(78%)の生成物を得た:1°C NMRs 27.837 (CH, CQ, C(C H, J), 7.7931 (CHC), C(CH), J), 37.752 (CHCH, CQ, J), 50.800 (NHCH), 64.212 (OCH, CH, OC(-CO)NH), 81.333 (CH, CQ, C(CH, J), ), 82.007 (CHC), C(CHQ, C(CH, J), ), 155.924 (OCH, CH, C), C(CH), 1, 169.674 (CH, CQ, C(CH, J), ), 169.969 (CHCQ, C(CH, J), ),

# [0120]

[実施例9] PEG-cmc-Asp-OH(12)

化合物11(15g, 0.375mmo1)をDOM(150mL)に溶解した後、TFA(75mL)を加えた。この溶液を 室温で2時間携拌し、ヘキサンで500mL)を加えて固体を沈殿させた。この固体をヘキサンで トリチュレートしてTFAを除去した後、冷却したDOM-エーテルで再結晶化させた。再結晶 化させた固体をDCM(150mL)に再溶解し、水(150mL)で洗浄した。有機層を分離し、無水均5 0,で乾燥させ、真空漫縮し、エーテルで沈殿させ、12.4g(83%)の生成物を得た; 1°C NMR<sub>8</sub> 36.441 (CHCH, CQ), 50.177 (NHCH), 64.390 (OCH, CH, OC(=0)NH), 81.333 (CH, CQ, C(CH, ),), 82.007 (CHCQ, C(CH,),), 156.172 (OCH, CH, OC(=0)NH), 171.944 (CH, CQ, C(CH,),), 172.211 (CHCQ, C(CH,),)。

## [0121]

[実施例10] Boc-Asp-Asp-OMe(15)

EDC・HC1(2,47g, 12.86mmo1)を無水DOM(30mL)およびDMF(2mL)中のBocNH-アスパラギン酸(13, 1g, 4.29mmo1)、アスパラギン酸ジメチルエステル・HC1(14, 1.86g, 9.43mmo1)、沿まびDMAP(2.47g, 12.86mmo1)の混合物を10元えた。この混合物を20温に一晩混めた。混合物を1N HC1で3回洗浄し、有機層を無水MgSO。で乾燥させた後、溶媒を真空除去し、生成物を得た(2.0g, 90%): H NMR& 1.45 (s, 9H)、2.62-3.02 (m, 6H, 3 x OH)、3.70 (s, 6H, 2 x OOH,)、3.74 (s, 3H, OOH,)、3.75 (s, 3H, OOH,)、4.50 (bs, 1H, OH)、4.85 (m, 2H, 2 x OH)、6.05 (d, J = 6.95 tz, 1H, NH), 6.98 (d, J = 8.05 tz, 1H, NH), 7 50

.57 (d, J = 7.69 Hz, 1H, NH).

[0122]

[実施例11] Asp-Asp-OMe(16)

化合物15(2.0g, 3.85mmo1)をDCM(30mL)およびTFA(15mL)に溶解し、溶液を室温で2時間提 押した。溶媒を真空除去し、残渣をDCM-エーテルで2回再結晶化させ、生成物(1.74g, 87%) かを白色の固体として得た:<sup>13</sup>C NMR & 35.52, 48.76, 50.12, 51.90, 51.96, 52.65, 114 .59, 118, 49, 168, 43, 170,02, 170,92, 171,17, 171,40, 171,48.

[0123]

[実施例12] PEG-cmc-Asp-Asp-OMe(17)

DMAP(4.5g, 36.86mmo1)を70CmLの無水クロロホルム中の9(分子供40,000,74g, 1.84mmo1) 10 および16(9.83g, 18.43mmo1)の溶液に加えた。この反応混合物を窒素下、24時間還流した。反応物を室温まで冷却し、濃縮して1/4の量にした。租生成物を2.5Lのエーテルで沈陵させ、濾過し、5.5LのIPA(65℃)で再結晶化させた。生成物を濾過し、新鮮なIPAで2回、新鮮なエーテルで2回洗浄し、40℃で一晩乾燥させ、59.0g(84%)の17を得た;11 C NMR & 3 5.344, 36.931, 48.082, 48.208, 50.835, 51.509, 52.239, 61.045, 63.953, 68.854-72 .056, 155.538, 170.102, 170.369, 170.453, 170.7346

[0124]

「実施例13] PEG-cmc-Asp-Asp-OH(18)

化合物17 (51g, 1.26mmo1)およびLiOH・H, O(0.8g, 18.9mmo1)を300mLの水に溶解し、溶液を室温で一晩機拌した。1M KTを加えて溶液の内を2.5に調整した。溶液をDMC3×600mL) 20 で抽出し、有機層を合し、無水MgSQ。で乾燥させ、真空違縮した。残液をDMCコ・テルで再結晶化させると生成物が得られた。これを濾過により回収し、40℃で一晩乾燥させ、38g(540)のオクタ酸(octa-acid)を得た; 13 C NMR (0,0) & 38.384, 39.704, 51.951, 54.465, 62.934, 67.105, 71.445-74.381 (PEG), 159.772, 173.831, 174.940, 176.359, 176.69 6。

[0 1 2 5]

[実施例14] <u>Mel-OMe(20)</u>

メルファラン(19, 1.00g, 3.28mmol)を2,2-ジメトキシプロバン(65.59mL, 533.49mmol)に 懸濁した。この懸濁液にHCJ水溶液(36%, 3.28mL)および無水メタノール(4mL)を加えた。 混合物を、溶液がわずかに褐変し込めるまで戦しく機件しながら穏やかに加温運流した後 、室温で18時間機拌した。反応混合物を真空濃縮し、残渣から粗生成物をエーデルで沈殿 させた。固体を濾過し、エーテルで洗浄し、シリカゲルカラムクロマトグラフィー(CHCL, 1MeOH = 9:1, v/v)により精製し、所望の生成物を得た(0.47g, 45%): 3 C NMR & 37.51, 40.340, 51.912, 53.435, 55.803, 112.124, 126.076, 130.620, 145.033, 175.754。

[0126]

「実施例15] Boc-TML1 & -Me1-OMe(22)

(天流物15) <u>805C-Int.13-ne: I-twic.22</u> (大変が15) <u>805C-Int.13-ne: I-twic.22</u> (大変が15) <u>805C-Int.13-ne: I-twic.22</u> (大変が15) またのMP(0.988g, 8.10mmol)を無水DM(15mL)および無水DM(15mL) および無水DM(15mL) からに 25mL 1 N HClで3回洗浄した。 有機層を無水硫酸マグネシウムで乾燥させ、濃縮し、シ 40 リカゲルカラムクロマトグラフィー(酢酸エチル: ヘキサン = 7:3, V/V)により精製し、所 20 の上成砂を得た(0.757g, 80.8%): <sup>3</sup>C NMR 2 20.120, 25. 306, 28.294, 31.768, 35.42 7, 35.947, 36.669, 39.505, 40.311, 49.324, 51.959, 53.234, 53.453, 79.467, 112.0 95, 123.374, 125.169, 130.439, 132.856, 133.427, 136.666, 138.697, 145.091, 149.841, 156.0811, 170.888, 172.298,

[0 1 2 7]

[実施例16] TML18-Me7-OMe TFA塩(23)

化合物22(0.757g, 1.09mmo1)をDCM(5mL)およびTFA(2.5mL)中、金温で2時間境料した。こ の反応液を濃縮し、最少量のDCMに再溶解し、エーテルで沈酸させた。生成物を濾過によ り回収し、所望の生成物を得た(0.222g, 35.9%): 'C NMR (CDC1,+ U, U) 8 20:026, 25 50 .146, 31.738, 31.892, 35.271, 36.219, 39.163, 40.340, 49.006, 52.219, 53.396, 11 2.073, 123.260, 124.756, 130.377, 133.026, 133.180, 136.815, 138.595, 145.110, 1 49.283, 171.069, 171.619, 172.630.

[0128]

「実施例17] PEG-cmc-TML1g-Me1-OMe(24)

窒素下、無水DM((23ml)および無水DMF(6ml)中のPEC-cmc-Asp-Asp-O+(12, 1,6g, 0.0391mm ol)、23(0.277g, 0.391mmol)、EDC(0.076g, 0.391mmol)、およびDMAP(0.155g, 1.269mmol )の混合物を窒温で一晩幾拌した。この溶液を真空濃縮し、残渣を130ml IPAで再結晶化さ せ、生成物を得た(1.543g, 92.5%)。UVアッセイで測定した生成物中のメルファラン量は2 4.66重量%であった: 12.0 NMR & 19.642, 24.788, 31.175, 34.350, 35.975, 38.817, 39.9 10 05, 48.558, 51.553, 52.808, 60.897, 62.331, 65.145-72.878 (PEG), 111.394, 122.76 1, 124.425, 129.698, 132.105, 132.878, 135.804, 137.737, 144.316, 149.065, 160.4 32, 170.608, 171.598,

[0129]

[实施例18] Boc-TML1β-AraC(25)

無水ピリジン(85mL)中のÅra-C(1, 9.88g, 40.66mmol)、の溶液を無水ピリジン(200mL)中の2 1(4.0g, 10.17mmol)、hDET(5.49g, 40.66mmol)、bC(15.61g, 81.32mmol)、およびNMM(8.93mL, 8.21g, 81.32mmol)、8.3量りの混合物に加えた。窒素下、この反応混合物を40で48時間提拌した後、真空濃縮した。残渣をDOM(300mL)に再溶解し、水(100mL)で3回、0.1N H C(1(100mL)で2回洗浄した。有機廖を硫酸マグネシウムで乾燥させ、濃縮し、シリカゲルカ 20.4 カーワマトグラフィー (CHC1, 160M = 9:1, 1√2)により精製し、所望の生成物を住成ったのようと526;11 C NMR & 20.315, 25.560, 28.522, 31.660, 35.520, 36.200, 39.221, 50.239, 61.719, 75.171, 76.698, 79.635, 85.341, 88.052, 96.435, 122.894, 132.519, 133.190, 136.186, 138.007, 146.222, 149.109, 155.906, 162.191, 171.733,

[0130]

[実施例19] TML1g-AraC TFA塩(26)

化合物 25(3g, 4.85mmOl)をDCM(15mt)に溶解した後、0℃でTFA(7.5mt)を加えた。この反応混合物を0℃で1.2時間機単し、冷水冷中で真空機縮した。残渣をDCM-エーテルで沈慶させ、所望の生成物を得た(2.37g, 77%): '1°C MMR (CDC1, + CD, OD) & 20.0, 25.3, 31.5, 31.7, 35.0, 38.9, 50.2, 60.9, 75.1, 75.8, 85.7, 88.1, 94.9, 109.7, 113.5, 117.3, 12 30 1.1, 122.5, 132.6, 136.4, 138.4, 148.7, 149.5, 150.1, 159.2, 159.6, 160.1, 160.6, 161.1, 170.6, 172.7,

[0131]

[実施例20] PEG-cmc-Asp-Asp-TML1β-AraC、八量体(27)

化合物26および18を実施例18と同じ条件に付し、27を製造した。

[0132]

[実施例21] 化合物6aおよび6bのin vitroおよびin vivoデータ

この実施例では、in vivoおよびin vitroデータを示し、非改変Ara-Cと比較している。

[0133]

<u>in vivo</u>

胸腺欠損ヌードマウスにドナーマウスから採取したLX-1の4~5mm 組織片を皮下移植した。腫瘍トロカール部位を週2回観察し、触診できるものを週1回測定した。各マウスの腫瘍体積を観径器での二次元測定により朗づ、式:腫瘍体積 = (長さ×幅\*)/2により算出した。腫瘍が平均体積90mm に達したときに、マウスを非改変Ara-CおよびPEG-Ara-C化合物からなるそれらの試験群に分けた。腫瘍サイズ分布が均等になるようマウスを分類し、4-6マウス/群に耐分し、永久識別のため耳にバンチ穴を開けた。薬物を毎分約0.5mLの速度で尾部静脈から静脈投与した、93d×4(1、4、7および10日目)。化合物は、20mg/kg/ኞ号で尾部静脈から静脈投与した、93d×4(1、4、7および10日目)。化合物は、20mg/kg/ኞ号と応くなど、20mg/kg/ኞ号を下るおよび6b、40mg/kg/ኞ号量(衛性);6aおよび6b、40mg/kg/授与量(衛性);6aおよび6b、40mg/kg/授与量(容量))に近い値でも与えた。マウス重量および腫瘍サイズは試験開始時と、第4週まで週2回測定した。薬物の有効性は処置したマウスと处置してい 50

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ない対照マウス(ビヒクルなし)との腫瘍増殖の比較により判定した。比較基準として5種類の指標を用いた: (a)28日目における平均腫瘍体精(b)各腫瘍体構の試験開始時からの平均変化率; (c)対照群の腫瘍体積中央値が約800~1100mm に達したとき(対数増殖期)に測定した腫瘍体積の相対率(XT/C)(d)21日目における(~2000mm)腫瘍体積の相対率(XT/C)(d)21日目における(~2000mm)腫瘍体積の相対率(XT/C)

## 【0134】 結果

化合物6bはわずか20%の活性親化合物量で非改変Ara-Cよりも優れた抗腫瘍活性を示した。 また、化合物6aも有意な効果を示した。8T/Cは6bの値の約2倍であったが、それにもかか わらず、特に本発明の化合物がわずか20%の活性親化合物量で投与されたことを考慮すれ 10 ば、それは非改変Ara-Cと比較して都合がよい。

# 【表 1 】

化合物	t <sub>i/2</sub> (h)° ラット血漿	1C <sub>50</sub> (nM) * P388/0	LX-1 % T/C <sup>b</sup>
Ara-C	-	10	74. 0 (100mg/kg)
化合物 6a	2. 1	123	122 (20mg/kg)
化合物 fib	53	958	59. 3 (20mg/kg)

# [0135]

\*全ての試験は2連、37℃で行い、t<sub>/2</sub>はPEC誘導体の消失により測定した。測定値の標準偏差 = ±10%。

"平均ペースライン腫瘍体積は1000mm"であった。

#### [0136]

#### in vitroバイオアッセイ

P388/O(マウスリンパ系腫瘍、Southern Research Institute)細胞系を使用して一連のin vitroviイオアッセイを行い、非改変Ara-Cもよび化合物10のIC。を調べた。P388/0細胞を RPMI 1640倍地(Whittaker Bioproducts, Walkersville, Maryland)+10%FBS(Hyclone Inc., Logan UT)で培養した。パイオアッセイは抗生物質およびファンギゾンを含有するそれ ら各々の接地で行った。

## [0137]

Ara-CをDMSOに溶解し、培地で好適な濃度に希釈した。PEG-Ara-C化合物を水に溶解し、培地で好適な濃度に希釈した。

# [0138]

アッセイを96ウェルマイクロタイター細胞培養プレートで2連で行った。

#### . . . . .

化合物の2倍連続希釈をマイクロタイタープレートで行った。0.1%トリプシン/ベルセンを加えて37ででインキュベートすることにより細胞を分離した。10%FBSを含有する各細胞系に好適な培地を加えてトリプシンを不活性化した。マイクロタイタープレートの各ウェルに10,000個の細胞を加えた。3日後、代謝性標識色素Alamar Blueを製造業者のプロトコールに従って添加し、細胞増殖を測定した。試験化合物および参照化合物のIC。。値は上記に表で示している。

## [0140]

本発明の好ましい実施形態であると現在考えられるものを記載してきたが、当業者ならば 本発明の精神を逸脱しない限り、変形および改変をなしうることが分かるであろう。本発 明の真の範囲にあるかかる変形および改変の全てを請求することを意図するものである。 【図面の簡単な説明】

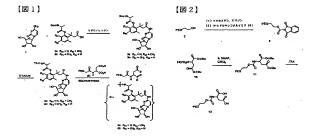
【0 1 4 1】 【図1】図1は、実施例1~6 で記載する本発明の化合物を製造する方法の概略図である

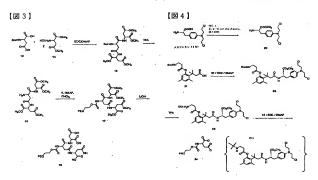
。 【図2】図2は、実施例7~9で記載する本発明の化合物を製造する方法の概略図である

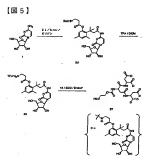
【図3】図3は、実施例10~13で記載する本発明の化合物を製造する方法の概略図である。

【図4】 図4は、実施例14~17で記載する本発明の化合物を製造する方法の概略図である。

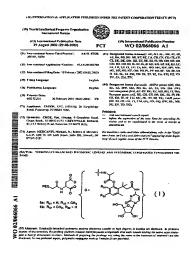
【図5】 図5は、実施例18~20で記載する本発明の化合物を製造する方法の概略図である。







# 【国際公開パンフレット】



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PCT/US02/04780

# TERMINALLY-BRANCHED POLYMERIC LINKERS AND

POLYMERIC CONJUGATES CONTAINING THE SAME

#### TECHNICAL PIELD

The present invention relates to new types of terminally-estimated polyments materials which are useful in forming long-eving conjugates of biosetive makeists. In particular, the treemon relates as polyments-based conjugates having starrased throughout purplement and methods of preparing the same.

### BACKGROUND OF THE INVENTION

Over the years, several methods of obtainmening biologically-afficient waterials to entercash have been proposed. Many medicinal agents are available as water-onbible salts and our in includation is performed to the contractions relatively easily. Problems arise when the destired medicinal segmit is closer insulable in appears. Bailed or in republy depending apply., Allabolak re-dent especially difficult is eschelistic.

One way to including we collected against a list include them as port of a stable profuse, products principle and a list including all weeks process recognised which, type softmicroscope, recognising them as the person compound in gings. Products are for extraction of collection of person of recognising and consumed by the transportation of centre of many time gings and no modely the transportation, distributions or michality of a deep in the body. Performment, against the constant of the collection of the coll

Produce ore often busingstally least or substantially macrive forms of the parent or source compound. The rate of release of the source drug, i.e. the rate of hydrolysis, is

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influenced by several factors but expossedly by the type of bood joining the parent drug to the modifier. Care must be taken to ryold propuring prodrugs which are difficiented through the lidney or real-rain endothelial system, etc. before a sufficient amount of hydrolysis of the parent compound occurs.

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homerwise; a before a spirid or producy from his hear appeared to morrest the criticating of left of a drug. However, is he have destinated the whon only you are not polymers of less than blood 10000 debase such less conjugated in critical liability states inclusiones such as allabilised compounds, for mainting conjugates are supply destinated less, on presiding it is associated phylodyse-critical less less as to his, and conjugates are as registly cleaned from the body data result if a hybridysiscome etter liabiles and cut of an except of less of the one of the other less of the other your etter liabiles and cut of an except destinated and one of the other than the other less of the other less of the other less of the other less of the other power state liabiles and cut of an except destinated and the other power of the liabile and other less of the other less of the other power of the liabile and the other less of the other less of the other power of the liabile and the other less of the other less of the other than the other less of the other less of the other than the other less of the other less of the other less of the other than the other less of the other le

therapeutic.

Camplatheria and misted biologically active analogs are often poorly water soluble and are examples of unbasance which would benefit from PEG profring technology. A brief or critics of easy presistan work in the field is presented below.

Olys, n. kl., J. <u>Binschiv. and Computible Photmess</u> Vol. 10 Jun., 1995, 51-66, dialoute describition PDG computes which we prepared by Linbing the two advertisents via venous linkage including seates. The unbendeds weaple of the PDG tool, however, is only about 5,000 at most. Thus, the <u>in view boards</u> we not fully related beause the computes was without any computes any advertisantly covered in the to additional blassic byfolloyist.

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Commonly-satisfied PCT publication WCR6/23794 describes his-occilington to which one copiralism of the hydrocyl-containing thing is structured to each terminal of the polymer. It upin of this advance, includent which would further increase the psystead of the polymet have been rought.

Then, there continues to be a need to provide artificiumal technologies for forming products of therepositio moretion such as camptothooto and related snadogs. The present irrection addresses this need.

### SUMMARY OF THE PAYENTION

In one aspect of the invention, compounds of Formula (1) are provided:

(1) 
$$R_1 = \begin{pmatrix} R_2 \\ C \\ R_3 \end{pmatrix} \begin{pmatrix} M \\ A \end{pmatrix}_{A} \begin{pmatrix} M \\ C \\ C \end{pmatrix}_{A} \begin{pmatrix} E_1 \\ E_2 \end{pmatrix}$$

R<sub>i</sub> is a polymeric renduc, Y<sub>i</sub> is O<sub>i</sub> S or NR<sub>i</sub>:

M is O, S or NR,

(un) is zero or a positive sategor, preferably 1 or 2; (a) is zero or one;

... / [1] \

E<sub>pe</sub> are independently 11, E<sub>i</sub> or

(a) and (p) are independently 0 or a positive integer;

Y<sub>1</sub>, are independently C<sub>i</sub>3 or NR<sub>1</sub>;

R<sub>NS</sub> we undependently releved from the group consisting of hydrogen, C<sub>i4</sub>

R<sub>NS</sub> we undependently releved from the group consisting of hydrogen, C<sub>i4</sub>

Riyés, C<sub>i4</sub>, translated allyde, C<sub>i4</sub> sychicalitys, C<sub>i4</sub>, rebetitered allyde, C<sub>i4</sub>, substituted allyde, C<sub>i4</sub> sychicalitys, translationed C<sub>i4</sub> heterocollyde, rebetitered C<sub>i4</sub> heterocollyde, rebetitered C<sub>i4</sub> heterocollyde, rebetitered C<sub>i4</sub> heterocollyde, respectively.

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atkyla,  $C_{i,d}$  alkony, phenoxy and  $C_{i,n}$  heteroalkony;  $D_i \text{ and } D_2 \text{ are independently OH,}$ 

or additional branching groups described below.

Within formulae (IV) and (V), (v) and (f) are independently  $\theta$  on a positive integer up to about 6 and preferably about 1;

 $k_1$  and  $k_2$  are independently at leased bifusetional finiters;  $Y_{s_1}$  are trajecuclearly selected from the group consisting of O, S and  $NR_{s_1}$ ;  $N_{s_{s_1} + 1}$  are independently selected from the group consisting of bybrogon,  $C_{s_2}$  align $(k_1, k_2)$  tensified all  $y_1 k_2 C_{s_2}$  when  $k_1 k_2 C_{s_3}$  which independently density  $k_1 C_{s_3}$  are individually  $k_1 C_{s_3}$  when  $k_1 k_3 C_{s_3}$  when  $k_2 k_3 C_{s_3}$  when  $k_1 k_3 C_{s_3}$  when  $k_2 k_3 C_{s_3}$  when  $k_1 k_3 C_{s_3}$  when  $k_1 k_3$ 

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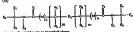
cycloalkyla, myta, substinuted aryls, aralleyls,  $C_{j,a}$  heteroalkyts, substituted  $C_{j,a}$  heteroalkyts,  $C_{j,a}$  alkezy, phenory and  $C_{j,a}$  hoteroalkyts,

At is a univery which when included in Formula (I) forms a multi-subtrinated records bydrocerbon or a multi-substituted interocyclic group; and

B, and D, are independently selected from the group contining of tearing groups, OB, residues of hydroxyl- or ambre-containing moisters.

In one porticularly preferred espect of the invention, the polymeric residue is also substituted on the detail partium with a modety of formula (31) below:

where all regished are an provision for fixed. Althoushood engagement are their formed when the polymeric resider (R.) includes both an eight act as comps fractional limiting group on that men, from or more equivalence of a biologically unitim-agent, drug or proton, design and beach as R, or Th, can be delivered. An example of anothe a biological proton of the contraction of the contraction



Yer purposes of the present invention, the term "recision" shall be understood to mean that portform of a biologically easiew compound which remains after the biologically active occupanted has undergone a substitution restricts in which the produce certifier portion has been statehed.

For purposes of the present invention, the term "ally/" shall be understood to include straight, branched, acknowing a c.g. halo, attenty, and retro,  $C_{1,0}$  allyin,  $C_{2,0}$  eyeloallyin or substituted cyclonilyin, etc.

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For purposes of the greated invertion, the term "substituted" shall be understreed to include adding or replacing one or more assess contributed within a functional group or compound with one or more different asserts.

For propose of the general correction, solutions subject include corrections, but including a subject to the proposed of the general control of the subject to the proposed of the subject to the subject

The term "sufficient encacks" for purposes of the present invention shall incan an arrount which schieves a throughout effect as such effect is understood by those of ordinary skill in the ret.

One of the shift-directages of the composate of the pressure invention in that the protops there is halfer privilege and the of physical that private intelligents. Bit generally spectred that the physical filter intensit to trimship had (PALI) based protop termination by Sporkhow that the termination termination for through termination or "smooth protops" money underspect handstrimen to repressure, for example, a motive yields in a case of the contraction of the protops that the contraction of the protops of the protops of the protops of the contraction of the protops of the protops of the protops of the contraction of the protops of the proto

Methods of making and using the compresses and our jugates described haroin are also provided.

BRIFF DESCRIPTION OF THE DRAWINGS

Figures 1 · 5 schematically illustrate methods of foresing compounds of the process invention which are described in the Examples.

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### DETAILED DESCRIPTION OF THE INVESTION

PORMULA (I)

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R, is a polymeric residu Y, is O, S or NR.; M is O. S or NR. (a) is zero or one;

(m) is zero or a positive integer;

(a) and (p) are independently 0 or a positive integer.

(4) and (p) see momentating of a positive integer.
Y<sub>1-a</sub> we independently O, 8 or NR<sub>ac</sub>:
R<sub>ing</sub> are independently obsessed from the group contristing of hydrogen,
C<sub>1-a</sub> slights, C<sub>3-3</sub> branched allyds, C<sub>1-a</sub> eyestentlyds, C<sub>1-a</sub> substriker cyclos lkyls, style, substituted myls, aralkyls, C., beteroolityls, substituted C., beteroalicyla,  $C_{3,6}$  alicoxy, planuxy and  $C_{6,6}$  betweethersy;  $D_1$  and  $D_2$  are independently OH,

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 $Y_{ad}$  are independently schemal from the group constating of O, S and  $NR_{1\beta}$ ,  $R_{11+1}$  we trelependently schemal from the group constating of hydrogen,  $C_{1a}$  alkyls,  $C_{1-1}$  branched alkyls,  $C_{3-1}$  excludingly,  $C_{1-1}$  alkyls,  $C_{3-1}$  branched alkyls,  $C_{3-1}$  submitted alkyls,  $C_{3-1}$  submitted alkyls,  $C_{3-1}$ elleyis,  $C_{i,q}$  altraxy, phenoxy and  $C_{i,q}$  heteroalizary: At is a mointy which when included in Formula (I) forms a multi-substituted

etic byda ocarbon or a multi-substituted heteromyolic group; and B, and H, are preferably independently solected from among inaving groups, OH,

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residues of hydroxyl-occasioning moisties or residues of amine-cont In another preferred embudiment, D, and D, are independently selected terminal

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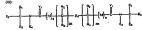
 $E_{\rm NN}$  are selected from the same group which defines  $E_{\rm L,i}$  above, except that while the definition,  $D_{\rm i}$  and  $D_{\rm j}$  are charged to  $D'_{\rm i}$  and  $D'_{\rm j}$  which are defined below.

Witin this embediatest, 11', and D', can be independently OH, a receipt of formula (IV) ∞ (v), or

whereth  $E_{\rm apol}$  are relected from the same group which defines  $E_{\rm apol}$  except that within the definition  $D_{i}$  and  $D_{i}$  are charged to  $D^{\alpha}_{i}$  and  $D^{\alpha}_{i}$  and  $D^{\alpha}_{i}$  independently OH, formula (IV) or formula (V). As can be appreciated from the above, when the terminal branching is taken to its failest extent with a bifunctional polymer  $R_{\nu}$ , up to sixteen (16) equivalents of drug can be loaded onto the polyments platform.

In those appears of this embediment where bit-substituted polyments residues are

derived, some preferred polymente muniport systems of the invention are shown below as



wherein all variables are as previously described.

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The multi-looding polymer transport system of the protess invention in based in large part on the polymer's proble acceptance forces on R., Optionsky, R., Secholes a capping group A. The polymer capping group A includes, for excepting interesting to lightcope, CO/H, Cu<sub>1</sub> skiyl mointee, and compounts of facusts (II) shown below, which forces a bead-system.

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whereir, all variables are as previously described. It will be understood and approxisted that the artificial terminal branching described above applies equally in the bit-systems as well. With regard to the other variables, which comprise the farmatee of the present

invention, the following are preferred:  $Y_{++} \text{ are each carypen};$   $R_{p++} \text{ and } R_{++} \text{ are each surface} \text{ lyndrogen or lower all $X_1$} \text{ c.g. } C_{++}$ 

R<sub>000</sub> and R<sub>10</sub> are each preferably hydrogen or sower: R<sub>10</sub>, R<sub>13</sub> and R<sub>14</sub> are preferably -Clk;

(m) is 1 or 2; (n) and (p) are each either pure or an integer from 1-4;

(v) is zero or 1;

(() is 1; L. is -(CHLCH\_O),-; and

 $L_i$  is one of  $AH_i$ ,  $AH_i$ 

## U. DESCRIPTION OF THE AT MOIETY

Rudering to Tormala (N, it can be seen that the Ar Is a makey, which when included in Formata (N, it can a make-pathetimed amounties hydrosetters on a make-pathetimed amounties hydrosetters on a make-pathetimed beautrapid group. A key feature in that of a ket awardery is exement in examinating the common of the section of the section

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the Fitchel rule (4 $\pm$ 12). Those of ordinary skill will realize that a myriad of motivies with uniaily the atomstic requirement of the motivity and thus are animable for one horon. Our particularly preferred averantic group is:

wherein  $R_{\rm th,20}$  are selected from the sense group which defines  $R_{\rm to}$ . Afternative status groups include:

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when its aid 2, and 2, as an independently Clap. or Village, and 2, il 0, 3 is 100, when When we selected from the case proper and the selection Page 2, or or years, the calencyl, and years and all an extra and the case and destined Page 2 is a comparison of the first finding or and the contemplated. It will take be appreciated by the service of adiatory ability that we consist triples are projected by the antimost of these arrows and 600, CRM, we see the context triples are quicked by the antimost of these arrows and 600, CRM, we see the gas influence of an antimost of the service of the arrows and the context of selection of the art. I always a projection of the service and the service are recording are an arrow of the service and the first of the projection of the proper recording are an arrow of the service and the first of the proper recording are applied of all fired give 3 in a 400 contributing coincides and the fifty. I make ye the time are desired arrows and the service are serviced as and the fifty.

#### C. DRUG GENERATION VIA HYDROLYSIS OF THE FRUDEEG The prodrug compounds of the present invention are designed so that the t<sub>10</sub> of hydrolysis is < t<sub>10</sub> olimination in planta.

hydrolysis in «U<sub>st</sub> solvanianes on pienten.

The linkinges included in the conceptuantle here hydrolysis sense in the pleases of the meanmal heing treated which is above enough to allow enflicient senouth of the present compounds, i.e. the transies or hydrolysi-constraints bloomist conspounds, in he relatesed prior to elimination. Some preferred compounds of the present invention have a v<sub>e</sub> for

prior to allimination. Some performed compounds of the present sevention have a  $t_{ij}$  for hydrohyds an plasme ranging floss about 5 minutes to about 12 hours. Perforably, the compositions have a plasme  $t_{ij}$  bybobysis ranging from about 0.5 to about 8 hours and most graferably flows about 1 to shout 6 hours.

### D. SUBSTANTIALLY NON-ANTIGENIC POLYMERS

As nazed above, R., is a worse volkide polymenic random which is preferably advantably non-emispecie such as polystylence and of PAOP or polymetries agreed (PEO). In preferate approx of the invention, Ps., further includes the previously sensitioned capting group, designated herein as A, which allows a bifurcionate or bre-polyment system to be formed.

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wherem Y, and Y, are independently O, S or NR<sub>00</sub> s as the degree of polymerization:

 $R_{13}$   $R_{2}$ , and  $R_{2}$  we independently selected from strong H,  $C_{1a}$  slightly,  $C_{1a}$  throughout alloyin,  $C_{2a}$  specialty,  $C_{2a}$  substituted ally in,  $C_{2a}$  substituted are substituted as substituted as substituted are substituted as substituted as substituted as substituted as substituted are substituted as substituted as substituted as substituted are substituted as subst

s and f are independently zero, one or two; and

A is a capping group.

The degree of polymerization for the polymer (A) can be from about 10 to about 2,500. This represents the number of repeating units in the polymer chain and is deposited on the indicate weight of the polymer. The (A) modern is a capping group as

defined heren, i.e. a group which is found on the instructed of the polyroot end, in some aspects, can be selected from any of 11, 11%, OE, CO, E, Co, a ship is order FPG terminal activiting groups, is each process or understood by these of ordinary skill.

Also useful are polyropyime glysols, banached PEG derivatives such as those

2.5 decrable for consensity seaged U.S. Proteo No. S.A.M.175. Case 3PEDF and strilling PLOS of such as those seaded in Elementer PLOS of the Psychophysics (Upon Elementer 1971 1897. The oblishment of each of this freezengs in incorporated lambs by strictions. It will be admirated on the season-built polyton costs of hardenshined for benchment of the Universities Plost on the standardshined.

to a further embodiment R<sub>t</sub> is optimally selected from among one or more of dextran polyvinyl alsohols, carbohydrate-based polymers, hydroxypropylanthactyd-

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armde, polyalkytene oxides, and/or copolymers thereof. See also commonly-estigned U.S. Parent No. 6,153,655, the continues of which are incorporated herein by reference.

- In many aspects of the presson in mention, Educationated polystolytess dysonia are postered when disc gase associated polystem originate are decised. Alternatively, polystolytess glyoted (PEGN), mass assistant, C., aftip-terminated polysiliphene conden (PAOI) such as mono-matthyl-terminated polystolytes glyoted (mEDOI) are preferred when mono-admont polystems are desired.
- he note as provide the desired hypothesis bilidate, mono- or diseal activated physics such as PEE acids or PE
  - Allowagh PAO's and PISO's on very substantially in reverge uncludard weight to polymorphism of the proteins a sine state about 2000 to weight everage in rows aspected of the invasion. Principle JR, is as weight soverage medicular weight of from where 20,000 in south 100,000 and care particularly from issued 250 to the shorted 6500. The everage sovietucian weight of the polymore detected for temberation to the proving must be sufficient to its province distillation expectation of the proper particularly as in the contract of the province distillation expectation of the proper particular production of the proper particular provincing where typically set the sufficients on the province distillation expectation of the proof particular production.
- The polyromic industance included barries or performly water-oublike at room to importance. A non-lineting his of each polyment brinche polysiliyates could been polyment usude as polysiliyates above. (PGO) or polymenylesse globol. polymy-tylysintaat polychi, persplyener thereof and bloks copyshpers thereof, provided that the water colcivities of the later quoylepser in minimized.
  - As an alternative to PAO-based polyssers, effectively new-antigeate meterials such as decurse, polyviny likebolus, embolystisch-based polytoers, hydroxysropylmethaurylatmoid (HEPAA), and copelymers thereof etc. and the libs can be tred if the same type of activation is employed as described better for PAOS such as

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PEG. These of auditury skill in the set will realize that the foregoing his attempty illustrative and the 1st polymeric materials having the qualities described better in reconstructurated. The propuses of the present investion, "Merchanty to an entire first "auditurative it propuses of the present investion," in a "and the polymeric materials under stood to the cert as being informatively one-unise and not eliciting on appreciable instance repose as in materials.

It will be clear from the foregring that other polyalitylene custle derivatives of the foregoing, such as the polyanopylene physical aride, etc., so well as other bi-functional insking groups are also contemplated.

### O E. PRODRUG CANDIDATES

#### 1. Residues of Hydroxyl-containing Compound

Committeein god Related Tanoisesterase. I historien
Committeein is a writte-insoluble systemic islanded produced by Committee occuminate trees indigenous to Chris and nothepodytes foreide meet indigenous to Chris and nothepodytes foreide meet indigenous to Relia.

occuminator trees indigenous to Chras and notherpoten gloridar trees indigenous to fadia, Computitisein and related compounds and makespar see that shares to be pointed as subsence or serbituants agents and how been shown to activité these softwares in artificial highlys. Computational soul related computants are also carefidates for conversion to the provings of the present invention.

Comptothecis and certain related analogues show the structure

Prom this over minutes, reveral howes satisfy have been prepared. For experience, the Arring is other to both of the 10- and 11-positions ten to be substituted with an OLI. The Arring case this be substituted in the P-spontium with a consigle or hemothest  $C_{\rm los}$  Bitly or  $C_{\rm los}$  Bitle  $C_{\rm los}$  Bitle

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colonistics, Johnson' princissis describations, sations, sations, validay, des Other admittations are produced for the CLD and first pages, first presented. A Partier Most. ASIA,1786, 4.95.3,778; Re 23,5118, the restreate of which are incorporated formin by reference. Sould described uses set to find using burners produced, exhibitions without worker experimentarion. Furthand comprehence formerine for our bases in stellar does which between 25-000 are authors of which workers which is applied for excising desirably with accurate allowed and produce to restrict the control of the contr

10 Reference to computative in makings herein has been made for purposes of illustration and not limitation.

Teamer and Pacificant Derivatives One class of compounds is aluded in the precing compositions of the present invention is taxanes. For proposes of the present invention, the term "taxane" includes all compends within the usane family of terpence. Thus, taxol (published), 3'-exheritated 16 and business component common derivatives (texasteres) and the bits as well as other statiogs which are readily symbosisms using standard organic techniques or are available from commercial accrecs such as Sigms Chemical of St. Louis, Missouri are within the scope of the present invention. These derivatives have been found to be effective anti-cancer agents. Numerous studies indicate that the agents have activity against neveral 20 malignancies. To dote, their use has been severely limited by, among other things, their short supply, poor water solubility and a tendency to cause hypermunitivity. It is to be understood that other taxones including the 7-aryl-cerbonates and 7-cerborates disclosed in community senigoed U.S. Pasent Nos. 5,622,986 and 5,547,981 cap also be included in the products of the present invention. The contents of the foregoing U.S. pateuts are incorporated herein by reference. Pacificael is a preferred texase.

c. Additional Riolecketh-Anties Moistifet. In addition to the foregoing molecules, the prodrag formicistions of the present invention can be prepared using many other compounds. For example, biologically-outlee compounds such as this-PEO conjugates derived from compounds such as

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The press composed without for profing from sent on he substantially were calculate, laishood for profits of the press where the profits of the press in receiving of the press in receivable and expension of the press of the press of the press of the press of the profits of the press o

The foregoing is Thurstier of the hologophy well we mode to which are hologophy for the products which are subject to find the products of the total being follow the meaning and the products of the total being follow products are not produced by the products of the product products of the products of the products of the first products of the products products on the products of t

In some ampects of the invention, B, or B, is a residue of an antine-containing composed, non-timeling list of each antible compounds include residues of organic compounds, compose, portain, polypointed, see. Organic compounds footbody, without limitation, motories such as antizeropiline compounds including demonshirely, described by a principalities nature; an explanta, ACAC (Systels are relieved) and described by a miseralized nature; and updatas, ACAC (Systels are relieved) and

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rchard anii-assabolise compounda, e.g., practitabins, etc. Ahrenstively, B can be a realizione di la socian-cominista conformational regres, uni sonoglassici, esti districtiva, statifungai such so organiza con conformatica più a, suri-assably esse proteoriserional quericitati sorrecci person-scrivintiq apras, assalgenio, fortility apras, courinesprire agent, ratio-informationy groot, servediot gent, suit-erconsis agunt, vayodibiling apent, vanconstrivintiq agent, des.

In a performal space of the increasing, the matter continuing composed in the size of the restriction of singuised, see in the transless, i.e., a reservation, including learness, for continuous for which the size in the transless of interests. In creation, i.e., the reservation is for which the size interest in the interesting for the compounds which can be anothered. Those of ordinary ability will quality them that which we proposed in the limit interpretability would find without reservations that it will be understanded for these belongisted by existing the same proposed as the laministic product and included an interpretability monthless desirable products and in the product in the size of the size of

The only failurations on the types of mathor constraining materials and while for including horizin. In that there is writible is hast one (primary or excounting) mathorization which can rest used that when it carrier portion and that there is not substrated loss of bisocitivity after the product system releases and separate to the primary configuration.

20 It is most that person compounds similarly for temperature in the appending composition of the investion, any extramedral the internationary personal shades the text extra when he helds the composition, but which will become sortion their wedge-paid a factor determine produced sense. For exemption, but which will become sortion that is delibered to the helds the become sortion of the sortio

#### 3. Leaving Chrosps

In these aspects where II, or B<sub>0</sub> is a terving group, exitable leaving groups include, without limitations, mointan each as k-k-yd-over-terminarizable, histogram, his-prince/phicalizable, positrophenosty, insidanable, N-Maydrouy-section-indy: this-assistant those, or other good having groups as will be apparent to those of ordinary

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skill. The synthesis resource used and described berein will be understood by those of

ordinary shill without undus experimentation.

For example, an anythird intermediate of compound (I) can be reacted with a reactual ruch as 4-circophosyl oblionformate, dissocializedyl carbonate (DSC),

reactant such as 4-eiscophonyl chloroformate, disaccinimidyl carbosate (DSC), carbosyldilimidasole, chiazolidiae thiose, etc. to provide the desired activated derivative. The solective acyletics of the phenotic or enlimic portion of the

p-lythoxybennyl alzobal or the p-aminokomyl alzobal and the o-hydrazbouryl alzobal or the o-wastocoxyl kloshul un be carried on wish, for example, distantibilet alzom devictioned polymers, consciously alrobates invited polymers, received polymers, blocked maleo and derivatives. Once in place, the "necivoso" form of the FIG: producy (or blocked myrdug) is mady for conjugation with an amino- or hydroxylcraticing, comparation, or constitution of the confusion of the confusion

## F. SYNTHESIS OF THE POLYMERIC PRODRUG TRANSPORT SYSTEM

Symbolis of representation polymer products in a first in the Suzuplus. Generally, however, in our perfector devoled for propusing the product passors represent, the polymer certains in from establest in the hemothing promps. Separately, the Mological Polymer and exter molety or deep, a Deep Colf for Pape MI, (e), the y. of the minist, is the standered on the TML component which may also include a Ministeriously query thereon as print or standarders to be pulsars. Next, the polymer transit on completing the certainal branches in second with the drug-TML pre-tree variety confidence and file-less to form the final product.

Indicates of the bifurciates apare containing its Tydl. Prog component to the polymer parties in grantisty careful out in the pressure of society great. As no-lineting list of ministre coupling again tolobe 1,3-discongrephen-bifurciate (DDPC), against absorbable in tide cycle and applicate (DDPC) against absorbable in tide cycle application (DDPC) against absorbable in tide cycle and applicate (DDPC) against absorbable in tide cycle and applicate (DDPC) against absorbable in the cycle and application (DDPC) against a solid application (DDPC). The cycle and application (DDPC) against a solid application (DDPC) against a solid a

Preferably the substituents are reasted in an inert solvent such as methylone chloride, chloroform, DMF or mixtures thereof. The reaction also preferably is conducted

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in the presence of a base, such as directly luminopyridite, dileogropylethylemine, pyridine, triethylemine, etc. to rectanize any solds generated and at a temperature flor O'C up to about 22°C (recent temperature).

O'C up to about 22°C (room temperature).

More perticularly, one method of perparing a polymerin transport system includes reacting a compound of the formula (VIII):

wherein all variables are as previously defined and B', is a residue of a bythunyl- or an amine-containing moiety;

with a compound of the formula (DX):

 $R_1 = \begin{bmatrix} \frac{R_2}{L_3} \\ \frac{R_3}{L_3} \end{bmatrix}_{00} \begin{bmatrix} M \\ A \end{bmatrix}_{10} \begin{bmatrix} \frac{1}{L_3} \\ \frac{1}{L_3} \\ \frac{1}{L_3} \end{bmatrix}_{00} = \frac{1}{L_3}$ 

wherein  $B_i$  is a polymeric residus  $Y_i$  to  $O_i$  to  $W_i M_i$  to  $O_i$  to  $W_{i+1}$  (o) is zero or one, (m) to  $O_i$  a power's energy  $Y_i$ , are independently  $O_i$  for  $W_{i+1}$  and  $W_{i+1}$  or independently of another order of  $W_i$  to  $W_i$  and  $W_i$  are independently energed down the group constraint of Polymers,  $W_i$  is,  $W_i$  in  $W_i$  is remoded ally in  $G_i$  cyclosity  $V_i$ ,  $G_{i+1}$  is substituted by in  $V_i$ ,  $W_i$  is a positive of  $W_i$  in  $W_i$  in  $W_i$  in  $W_i$  in  $W_i$  in  $W_i$  is a positive of  $W_i$  in  $W_i$ 

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k, is 
$$-\left(\begin{array}{c} 1\\1\\1\\1\end{array}\right)_{0}^{2}$$

E. are independently H. E., or

wherein D, and D, are independently OH or a leaving group which is capable of centing with an expectacted arrive or hydroxyl or a terminal breaching group; (n) and (p) are independently 0 or a positive integer;

Y<sub>24</sub> are independently O, S or NR<sub>m</sub> and

 $R_{e_{10}}$  are independently selected from the group consisting of hydrogen,  $C_{14}$  alkyls,  $C_{34}$  branched alkyls,  $C_{34}$  cyclealityls,  $C_{14}$  submitted alkyls,  $C_{34}$  substituted eyelenlikyla, aryla, substituted aryla, aralkyla,  $C_{t,\epsilon}$  betereolityfa, substituted  $C_{t,\epsilon}$  betereallryls, C., olkoxy, phenoxy and C., a hoteroalkoxy;

In further septems of the motion),  $D_0$  and  $D_0$  are independently selected terminal incombing groups of formula (X)

where  $E_{t,i:t}$  are selected from the same group which defines  $E_{t,i:t}$  except that  $D_t$  and  $D_s$  are changed to  $D^*_t$  and  $D^*_s$  which are defined below. Within this embediaton,  $D^*_t$  and D', can be independently CH, a molety of farmula (IV) or (V), or (XI)

wherein  $F_{q,s,qq}$  are selected from the same group which defines  $K_{p^{s}q}$  except that  $D_{s}$  and  $D_{s}$ are changed to D", and D", which are defined as being independently Oil or a leaving group which is capable of morting with an unprotected emine or hydroxyl.

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Such symbotic techniques allow up to sixteen (16) captivalents of carboxylic soid or activated carboxylic soid, for exemple, to be attacked. As shown in the preferred structures herein, PEG veridues with tennically branched mobil-acids are preferred espects

Regardless of the synthesis selected, some of the preferred compounds which result from the synthesis techniques described herein include:

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wherein R, in a polymer residus such as a PAG or FEG and D is OH, femnels (IV) or (V Preferably, D is

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In another preferred aspect of the inventi-tion are of formula (XII):

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#### wherein all variables are as previously defined above.

### G. AN ATPROPRIACES OF THESE

A further separ of the trunction periodic the conjugates of the nomine quicked properties of the displayable to place the transpare classical above, wherein the tap is believed the displayable or lengting tempore. Thus, a missiste tap is proposed by brighting on purishers come; July as much used streamy, any own redunderd cattering interes, rather-special belt transpared interession includes the case and examinetaries beltes retained for magnetic reasonate insigning, flowerserversion beltes, balled cattering interest, rather-special interest transpared transpared balls, and the contraction of the confidence of the first transpared to the sand failed in a configurate theraposite resisting, before the transpared to the sand failed in a configurate theraposite resisting, before the transpared to the sand failed in a configurate theraposite resisting, whereig for measuring of the distribution of a theraposite behalpingly with resemble value in any minimal transpared.

In a still future report of the invention, the boronion begade engineers are small proported, by the shown extends,  $\psi$ , we pushable black, industing,  $\Delta$ , and/sintenge, blacks. Simply by way of controls, these include, "Busines, "Busines, "Business, "

Thready, for manifold localitation of famous times is a patient, the compants ago in efficiently on patients or mind supposed of lawing a masser, where stilleden stone on above the stolend featurement, below to because it the uses with the plainty and present 10 air facilit is detected, for imasser, viewly, by X-ray subspaying, companished somestical incompanished, CMC, by international stores of a facilitation of the play places accurate devices such as a games contact, or any other trackford or extraction appropriate for facilitation of the selected sign.

The dotected rignal is then converted to us image or seatomical and/or physiological determination of the turnor site. The image makes it possible to locate the turnor in vivo and to dayine an appropriate thempositic strategy. In those embodicecats

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where the tagged rankery is itself a threspenic agents, the demend agent provides evidence of anaecenical localization during treatment, providing a baseline for follow-up diagnostic and therepeotic interventions.

#### 11. METHODS OF TREATMENT

Another report of the pressed invention provides tradebad of treatment for write models conduction in manufact. The methods include definitioning in the meanmal in model of noth returness, as efficient enterior of produce, such as a mini-lored Arta C-PEC ossippation, which has been prepared as described branks. The competitions are model first, more discontine dischers, whething returns of models dischers, whething returns a method preventing ecourates of transhroophenial growths in manufacts.

The Statutes of the profits againstrate with deposed upon the power methods to be tracted or change, for contract of contract power and the tracted traction. Generally, the tracted or change and the restrict an establish to tensional studies, differently address and the change of the restrict power contracted to the profits or change of the restrict power contracted to the profits or change of the restrict power contracted to the profits or change of the restrict power contracted to explore a restrict power of the profits of the profit power of the profits of the profit

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Such oderiustration may also be by influsion into a body space or cavity, as well as by inhalation end/or intransal routes. In preferred sepacts of the promision, however, the products are parenteedly administrated to recramata in peod thereof.

#### 1 ENAMPLES

- The following exemples serve to provide further approximen of the invention but are not meant to any way to restrict the effective scripe of the invention. The underlined and bold-faced numbers registed in the Electropic correspond to those shown in Figures 1—
- General, All restriction were then often an immediate and the processing of the processing of the comment of the processing of the comment of
  - JIFLA SMEAS. Analytical IMPCA's very portround using a CP reserved photo solution. (Reclaims, Reclaims) under insertice conference with on 1000 miles relief by a methanol-water or mobile place. Proble designs were received at 156 mm cating a 170 mm. Contact. To desire they presented of the Pref Dougla lable to undership the presence of PROVEATION product, on emporation high restricting desirence (ELDPS), Model Pro-Dalled SMEAS (SP) (Pulser Laboration), were employee and the LAD and the Versich works), and the fault PRO-Juned products were then of native dwag and were 3 29% part by IREA. Analytic of ALM Contacts in PRO Destriction. For the determination of the series.
  - content in PTG derivatives, if a cryphysidise was used as a nacide. The UV shortware of if a content in PTG derivatives, if a cryphysidise was used as a nacide. The UV shortware of if a content in ptg in the content in the in the conte

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standard in 11/20 cm approximate concentration of 0.013 yearshool, these for a NEV 60 of 11/10 year for 10 yearshood of 12/20 rouse a formation. Using this was and employing the description coefficiency, a debated from the above, the concentration of earth c in the semple of the concentration of earth c in the semple occurrentation d earth d in the d in the semple occurrent and d earth d in the d in th

michinais in the sample was determined. Dividing that while by the sample concernment provided for processing of michinals in the sample. Abbreviations. DCAI (disablescentilinus). DMAP (4 (disording learning-legislate), DDC (1etay-5-1-disording-imminesprophysolrodilinutida), IVOIT (1-by-descriptoserizately). DA (Dgregous), NSAM (6/mattripuspolyboar). TA (pridravenestic said).

Example 3. A contine of era C (1, 17) g 7,12 zonol), 2a (700 ag. 1,17 z

31.51, 31.96, 39.57, 50.18, 50.45, 61.88, 74.50, 80.15, 85.90, 88.58, 96.25, 122.51, 29

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132.82, 133.34, 136.73. 138.22, 146.57, 149.90, 155.65, 155.96, 162.08, 171.89, 174.06. Example 2.

Compared 3b. Compound I was coupled with 2b using a similar condition as in Example 1 to produce 36 in 54% yield: "C NMR 6\_17:23, 17:92, 18:33, 25:49, 28:32, 31.51, 31.58, 31.99, 32.46, 39.52, 40.09, 50.08, 50.22, 61.72, 74.50, 74.94, 80.11, 80.15,

- 85.45, 55.90, 88.01, 58.38, 96.25, 122.51, 126.77, 129.03, 129.16, 131.68, 132.82, 136.24, 136.73, 138.22, 146.05, 146.57, 149.90, 255.65, 155.96, 171.85, 171.89, 174.96. Example 3.
- Comprised 4s. Compound 3s (638.8 mg, 1.03 merel) was stirred in solnyhous DCM (6 mL) and TFA (4 mL) at room temperature for 2 h. Ethyl other was added to the solution 10 to precipitate the creeks product which was filtered and weeked with other to give 4a as a whate rollid (534.5 mg, 62%); "H NMR (DMSO-4), 8 1.52 (s, 311, (CH,),CH) 1.55 (s, 3H, (CE<sub>4</sub>),CH), 1.62 (d, 1 H, J = 8.1 Hz, (CH<sub>2</sub>),CH), 2.22 (e, 3H, CH<sub>2</sub>Ar), 2.57 (e. 3H, CB\_Ar), 2.97 (a. 28, CH\_C(=O)), 3.41-4.27 (m, 5 H, sm-C's H-2'-H5'), 6.09 (d, 1R,
- J = 5A, ana-C + H-1"), 6.67 (a, 1 H, An-H), 6.90 (a, 1 H, An-H), 7.12 (d, J = 5A, H-6), 8.05 15 (d, J=8.1, H-5), 8.67 fbs, 1H, YFA); "C NMR (DMSO-4) 8 15.45, 19.67, 24.97, 31-05. 31.23. 38.56, 40.41, 48.53, 49.02, 61.02, 64.94, 74.64, 76.14, 85.74, 86.95, 94.32, 122.32, 132.41, 134.68, 135.67, 138.00, 146.71, 149.20, 154.50, 158.21, 158.72, 162.02, 169.68, 171,87. Example 4.
- 20

Compound 4b. Compound 3b was subjected to the same condition as in Exemple 3 to give 46 in 82% yield: "H NMR (DMSO-4) 8\_1.52 (s, 3H, (CIL), CH) 1.55 (s, 3H, (CH,),CH), 1.62 (d, 1 H, J = 8.1 Hs, (CH,),CH), 2.22 (s, 3H, CH,As), 2.57 (s, 3H, CHAY), 2.97 (s. 2R. CR.CO-O)), 3.41-4.27 (m. 5 Ti. sm-C's R-2'-R5'), 6.09 (d. 1R.

- 18 J = 5.4. am-C's H-1"), 6.67 (a, 121, Ar-H), 6.90 (a, 131, Ar-H), 7.12 (d, J-5.4, H-6), 8.05 (d, J=R.1, H-5), R-67 (bs, 1H, TFA); "C MAR (DMSO-4) 8, 35.45, 19.67, 24.97, 31.05, 31,23, 38,56, 40,41, 48,53, 49,02, 61,02, 64,94,74,64, 76,14, 65,74, 86,95, 94,32, 122,32, 132.41, 134.08, 135.67, 138.09, 146.71, 149.20, 154.50, 156.23, 158.72, 162.02, 169.68, 171.67. 30
  - Exemple 5. Compound 6a. A mixture of PEG-aspartic sold (mw. 40,000, 5, 3 g, 0.074 mm·l), 4e (185.6 mg, 0.74 mmol), NMM (240 mg, 2.38 mmol), HOBT (120.5 mg, 0.69 mmol), and

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EDC-HCI (228.4 mg, 1.19 mmol) in anhydrous DCM (50 mL) was stirred at 0 \*C for 30 nrivator. The reaction was allowed to werm to room tomperature and continued for 3 days and filtered. The filtrate was consentrated in verse and the residue recrystallized from IPA to give 2.7 g (50%) of product. The manual of sro-C in the product measured by UV assay was 2.11 wild: "C NMR 8 14.40, 19.22, 24.56, 31.17, 38.26, 38.90, 47.94, 48.67, 49.66, 60.17, 61.12, 61.90, 67.86-70.87 (PEG), 71.70, 74.50. 85.01, 87.53, 95.28, 121.39, 131.18, 132.68, 133.19, 134.77, 137.70, 145.26, 138.93, 155.23, 160.12, 161.56, 168.39, 170.72, 170.92, 171.27, 171.34. Raampte 6.

Compound 6b. Compound 4b was subjected to the same condition as in Example 5 to give 6b in 88% yield. The amount of ara-C in the product measured by UV samy was 10 1.68 w/5: "C NMR n 15.12, 16.22, 24.52, 24.73. 29.55, 30.55, 31.15, 36.04, 38.59, 47.66, 49.16, 49.93, 50.18, 60.93, 61.12, 62.90, 69.44-71.59 (PLG), 71.70, 74.50, 84.78, 84.50, 87.53, 94.85, 127.60, 130.20, 135.51, 136.10, 141.70, 145.15, 147.50, 155.00. 161.20, 169.47, 170.62, 170.92, 171.27.

Example 7. Compressed 9. PSG diel (7, 55 g., 1.38 ressol) was accorroped in tolerase over a 2 hour period followed by removel of 200 mL of solvent by rotary evaporation. The solution was couled to -50 °C and triphospene (0.544 g. 1.83 mmol) was added as solid followed by minydrous pyridine (0.414 g. 5.49 mmol), and the reaction minters stiered at 50 °C for 1 hour. N-hydroxyphthahmide (6, 1.12 g. 6.88 musel) and enhydrous pyridine (0.54 g. 6.88 named) were added to the chloresformate maxture and the reaction stirred for a further  ${\bf 2}$ hours at 50 °C then for 12 hours at room temperature. The reaction mixture was filtered through filter paper and the solvent removed in success and the product crystallized from methylane chloride-ethyl other (1100 mL, 1:2, v/v) to give the product (50.9 g. 92%): 25 <sup>14</sup>C NMR 5 123.62, 128.10, 134.55, 152.00, 169.00. Example 8.

FEQ-ent-Asp-Q-#-Bu (11). Compound 9 (mw. 40.000, 20 g. 0.459 mmol) and separtic acid di r-butyi uster IICI (10, 1.0 g, 3.55 mmol) were dissolved in anhydrous IXCM, 30

Indicated by addition of UMAP (0.433 g, 3.55 mmol). The solution was reflexed overnight followed by procipitation by addition of ethyl other (1 L). The solid was instituted by ribration and recrystalized from IPA (1 L) twice. The filter cake was created

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Example 1.1.

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with IPA (100 ml.) and other (700 ml.) to give 15.6 g (78%) of product after drying at 45 \*\*Cla views \*\*C. Note 8.77.877 (CHCCA/CRIS), 27.791 (CHCA/CA/CRIS), 27.792 (CHCA/CA/CRIS), 27.793 (CHCA/CA/CRIS), 27.793 (CHCA/CA/CRIS), 27.90 (CHCA/CA/CRIS), 25.90 (CHCA/CA/CRIS), 25.90 (CHCA/CA/CRIS), 15.904 (CHCA/CRIS), 16.905 (CHCA/

passage of Pliki-ema-Aup-OB (12). Compound 11 (15 g. 0.375 mmil) was dismbred in DCM (150 ml.) followed by the addition of TVA (75 ml.). The relation was alread at roses recognition for a boson as of bosons (250 ml.) belief to prepriction the cold. The solid one trimentod with bosons to remove TVA followed by recognitization thus childred DCM-cflor. The recognition to cold was refused by a form the DCM (250 ml.) and washed with bosons to remove TVA followed by recognitization thus childred DCM-cflor. The recognition foul was refused by the DCM (250 ml.) and washed with bosons to remove TVA followed by recognition that the propriet (150 ml.) The regard (150 ml.) The regard

connectated is man, and principlisad with class to give 12.4 g (RM) of product 'C 1958 8 58.441 (GTGL)CO., 56.177 රාම(FI), 64.356 (CGE),CB),OC-O),RB), 11.51 (GTG,CA),CFG),J, 12.007 (CFGC),GCG),J, 154.172 (O-09),GH,OT-O),PBP), 171.44 (CE),CG,CGE),J, 172.211 (CSGC),CGE),J.) Emergie 10.

The August App CMM (19) S. IDC-101 (2.47 ± 2.18 km moly has acide to a smaller of a BodTell-expect seed (2.1 ± 4.28 km moly has acide to be smaller of a 200 km moly control (2.41 ± 6.18 km mol) in subject so IDC-20 (2.01 ± 0.20 km mol) in subject so IDC-20 (2.01 ± 0.20 km mol) in subject so except the DE-20 (2.01 ± 0.20 km mol) in subject so except so in subject so except with DE-20 (2.01 ± 0.20 km mol) in subject so except so in the DE-20 (2.01 ± 0.20 km mol) in subject so except with DE-20 (2.01 ± 0.20 km mol) in subject so in the DE-20 (2.01 ± 0.20 km mol) in the DE-20 (2.01

Asp-Asp-Oble (16). Compound 15 (2.0 g. 3.85 month) was dissolved in DOM (00 mL) and TDA (15 mL) and Bre oblation was remard for 2 in a room temporature. The solvent was returned in throom soft for residence was recrusived motion of the room of the Chestico was recrusived motion with refer the product (1.74 g. 87%) as a white solide: "C Notife 3.35.2, 4.65, 50.12, 51.00, 51.56, 524.51, 11.95, 11.84, 11.64.31, 10.02, 17.00.27, 17.17, 17.19, 17.14.0, 17.14.6.

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#### Example 12.

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PEG-cms-Asp-Asp-OM+ (17). DMAP (4.5 g, 36.86 mone)) was added to a solution of 9 (row. 40,000, 74 g. 1.54 mms?) and 16 (9.83 g. 18.43 mms?) in 700ml. of enhydrous chiuruform. The reaction exhibits was reflected for 24 hours under nitrogue. The reaction was enoised to proops temperature and concentrated to 1/4 volume. Crude product was precipitated with 2.5 L of other, filtered and recrystallized from 5.5 L of IPA (65°C). The product was filtered and washed twice with fresh IPA, twice with fresh ether, and dried evernight at 40 °C to yield 59.0g (84%) of 17: "C NMR 635.344, 36.931, 48.662, 48.205, 50.635, 51.509, 52.239, 61.645, 63.963, 68.854-72.656, 155.538, 170.102, 170,369, 170,453, 170,734.

#### Example 13.

PEG-case-Asp-Asp-OII (18). Compound 17 (51 g. 1.26 mmsl) and LiOII-H<sub>2</sub>O (0.8 g. 12.9 mmol) were dissolved in 300 mL of water and the solution stirred oversight at soom temperature. The pH of the solution was adjusted in 2.5 by the addition of IN HCL. The 15 solution was extracted with DCM (3  $\times$  600 mL), the organic layers combined, dried over enhydrous MgSO, and concentrated in vector. The residue was recrystallized from DCMother to give the product which was collected by filtration and dried at 40 °C overnight to vield 38 a (54%) of the octa-sold: "C.NMR (D.Q) 8 38.384, 39.704, 51.951, 54.465, 02,934, 67.105, 73.445-74.381 (PEO), 159.772, 173.831, 174.940, 176.359, 176.696. 20 Example 14. Mel-OMe (10). Melahalan (19, 1.00 g. 3.25mmol) was suspended in 2,2 dimethoxypropure (65.59 m.L., 533.49 mmol). To the eutpensies was added aqueous RCI (36 %. 3.28 ml.) and absolute methanol (4 ml.). The mixture was warmed to mild reflux with

vigorous stirring until volution started to turn slightly brown, followed by stirring at ream 25 impereture for 18 hours. The reaction mixture was concentrated to vecue and the crude product precipitated from the residue with other. The solid was filtered, washed with tiher, and parified by alice gel column chromatography (CHCl, : MeOH = 9:1, wh) to yield the desired product (0.47g, 45%): <sup>16</sup>C NMR 6 39.751, 49.340, 51.912, 53.435, 55.603, 112.124, 126.076, 130.620, 145.033, 175.754. 30 Example 15.

# Rec-TM1.1p-Mct-CiMe (22). EDC (0.52 g. 2.70 mmol) and DMAP (0.968 g. 8.10 mmol) were added to a mixture of 21 (0 53) g. 1.35 rumol) and 20 (0.86) g. 2.70 mmol) in

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embelows CCA (13 rds), and analysis (24 rd C  $^{\circ}$  cal  $^{\circ}$  eV C in a size belo. The critical matter are with of a new temperature registry their dissipance from the constraints of a new temperature registry three of Stappen from constraints of a seaso. The mobile was undissolved in ECA (17 a) and valued free fines with 24 EAL, 18 MC The angives free with of the value free sizes with 24 EAL, 18 MC The angives free with of the value free sizes with 24 EAL, 18 MC The angives free with of the value free sizes with 24 EAL, 18 MC The angives free with 24 EAL, 18 MC and 18 The 24 MC and 18 The 24

- Energie 14. TAILL/SM-10M-17A Solt (23). Compound 12 (0.72)  $g_1$  100 mms) was attend to DCM (61d) and TM-62 s-12 in zono improvates for 2 leave. The reaction shotted to DCM (61d) and TM-62 s-12 in zono improvates for 2 leave. The reaction shotted in the concentration of the confidence of the confid
- Kanegh 17.

  FIG-ene-TML191M-6-UMs (20). A minure of FEG-ene-Aug-Aug-GII 0.1.1.6g.

  00 (1991 mml). 13 (0.77). 6.399 mml). IDC (0.776; 0.391 mml), and (104.07.135; 1.290 mml). The (107.07.10) mml). The (107.07.10) mml) of the (107.07.10) mml). The (107.07.10) mml) of the (107.07.10) mml) of the (107.07.10) mml). The (107.07.10) mml) of the (107.07.10) mml) of the (107.07.10) mml). The (107.07.10) mml) of the (107.07.10) mml) of the (107.07.10) mml). The (107.07.10) mml) of the (107.07.10) mml) of the (107.07.10) mml). The (107.07.10) mml) of the (107.07.10) mml) of the (107.07.10) mml). The (107.07.10) mml) of the (107.07.10) mml) of the (107.07.10) mml). The (107.07.10) mml) of the (107.07.10) mml) of the (107.07.10) mml). The (107.07.10) mml) of the (107.07.10) mml) of the (107.07.10) mml). The (107.07.10) mml) of the (107.07.10) mml) of the (107.07.10) mml). The (107.07.10) mml) of
- 135.504, 137.737, 144.316, 149.055, 166.482, 170.608, 171.596.
  Example 18.

  Bet-T931,1j-AraG (15). A solution of Ara-G (1, 545 g 40.66 mmol) in salpulmous
  prifiline (31 ml.) was added to a minister. at '11 (4 G g. 10.17 men/s). HIGHT (5.87 g 40.66
  mmol), TGC (15.4 g 1, 31.3 mm), and 13.64 (15.66, 21.5 g 1), 127.00-1, 8mg) in

solvychous pyridips (260 mL). The reaction mixture was solved for 46 bosos at 40  $^{\circ}\text{C}$  \$34

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Table tillings, fishiowed by construction to marsh. The midster was reliabled in DCM (OH CA), whence the times set to wars (100 mid) and roles with 63 mill (OH CA). The reprincipant of the region of

This January, The Sett (Ed), Compound 2016, a 427 mostly was dissolved in Deciding Vision 12 to 4 (Compound 2016, a 427 mostly was dissolved to 4 (Color Color Col

Example 20.

In Vivo

PEG-cmc-Asp-Asp-TMLIP-AraC, octsmer (27). Compounds 26 and 18 were subjected to the same condition as in Europle 18 to propere 27.

Example 21.

20 In vitro and in vitro data for compounds fin and 6b.

To this Example, in vivo and so vitro one see presented and compared to vamodified Are-C.

Adoption to the claim's was implained advantagement with a 4-5 and from the Regiment of EAS. Adoption that the claim is the basic section at the sub-contrast direct another and necessarily are produced by the claim of the claim is the claim contrast and the claim of the claim of the claim contrast and the claim of the claim's clai

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Ars-C was dissolved in DMSO and diluted to the appropriate researchism in culture media. The PEG-Ars-C compounds were dissolved in water and diluted in the appropriate concentrations in culture media.

The except were performed in displaced in 16 feet 1811 critically confidence of the confidence of the

While them have been described what we presently believed to be the preferred embediments of the increasing them shill be in the set will realize that changes and modification may be made window departing from the spirit of the invention. It is attended to claim all such changes and modifications as full within the true scope of the invention. WO 02/04/046

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#### WHAT IS CLAIMED IS:

# A compound comprising the formula

$$\begin{array}{c} 0) \\ \text{where, in:} \\ R_1 = 1 \text{-paly proper in module;} \\ M_2 = 0 \text{- for NML:} \\ M_3 \approx 0.5 \text{ or NML:} \\ B_1 = 0 \text{- for NML:} \\ B_2 = 0 \text{- for NML:} \\ B_3 = 0 \text{- for NML:} \\ B_4 = 0 \text{- f$$

(a) is stro or one;

(m) is zero or a posteive integer;

(a) and (p) are independently 0 or a positive unegar,  $Y_{1s}, are independently O, S or NR_{ns}$ 

3 to the interpretative V, 2 or 2 Nag.

R<sub>1</sub> is an independently selected from the group constraints of hydrogen,

C<sub>14</sub> slicks, C<sub>24</sub> branched allyle, C<sub>24</sub> exclosiogh, C<sub>14</sub> substanted allote, C<sub>24</sub> sobatises
cycloslogia, eryte, substituted style, analogia, C<sub>14</sub> betweenlogis, substituted C<sub>14</sub> between

cyclocikyła, czyła, substituted szyle, azalkyła,  $C_{t,a}$  betwoodkyła, substituted  $C_{t,a}$  bet alkyła,  $C_{t,a}$  alkowy, phenoxy and  $C_{t,a}$  betwoodkony: 1), and  $D_{t}$  are independently OH,

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or a recovered beneathing or on

wherein (v) and (t) are independently 0 or a positive integer up to about 6

Jis NR<sub>11</sub> or

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 $L_1$  and  $L_2$  are independently selected bitimutional historic

Y<sub>4.5</sub> are independently actored from the group consisting of G, S and NR<sub>4.7</sub>.

R<sub>1.6</sub> with independently actored from the group consisting at Bydreem, U<sub>4.6</sub> allylis C<sub>4.6</sub> beneficial clipts, C<sub>4.6</sub> arbeited displos, C<sub>6.6</sub> arbeited displos, C<sub>6.6</sub> arbeited displos, C<sub>8.6</sub> arbeited displosed d

At us a moiety which when included in Formula (f) forms a multi-substituted arountio hydrocarbon or a multi-substituted heterocyclic group;

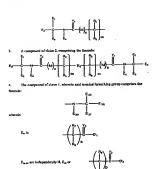
B, and B, are independently salvated from the group consisting of leaving groups, OH, residues of hydroxyl-contribing monitors or entire-containing monitors.

2. The compound of claim 1, wherein R, thefter computes a capping group A, schedul from the group conditing of hydrogen,  $NH_{\rm p}$ , OH,  $C_{\rm p}$ ,  $C_{\rm ref}$  monotics and

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(n) and (p) are independently 0 or a positive integer;  $Y_{j,k} \ are independently 0, S or NR_{ii};$   $R_{i,k} \ are independently as lected from the group consisting of hydrogen$  $C_{14}$  alkyla,  $C_{24}$  branched alkyla,  $C_{14}$  cyclonikyla,  $C_{14}$  substituted alkyla,  $C_{5}$ , sub cyclonlicyle, cryle, substituted cryle, arelicyle, C,, beteroolkyle, substituted C, , betero-

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alkyls,  $C_{14}$  allomy, phenoxy and  $C_{14}$  beteroxikoxy;  $O^*_{11}$  and  $D^*_{22}$  are independently OH.

wherein (v) and (i) are independently 0 or a positive suitger up to about 0;  $L_1 \ {\rm and} \ L_2 \ {\rm are} \ {\rm independently} \ {\rm selected} \ {\rm bifunctional \ linkers};$ 

is, in the I<sub>1</sub>, sive contended this detailed linkers:

Y<sub>1</sub> are inclopendately selected from the pump consisting of O<sub>1</sub>, 8 and 100<sub>1-2</sub>

R<sub>11...</sub> we independently selected firm that group consisting of hydrogen,

C<sub>1</sub>, a blayfs, C<sub>1</sub>, a branched of layfet, C<sub>2</sub>, or backlete, C<sub>1</sub>, a restricted allylet, C<sub>2</sub>, a chaintee

opticallylet, hydrogen delight, C<sub>2</sub>, a firm could be a become,

allylet, C<sub>2</sub>, a blancy, phenory and C<sub>10...</sub> between layer.

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Ar is a nactory which whose included in Forensia (1) forms a multi-substituted matic hydrocorhoo or a multi-substituted hearmoyetic group;

B, and B, are independently selected from the group consisting of leaving groups

III, residues of hydroxyl-containing moleties or amino-containing moietics;

D", and D", are independently O

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- 5. The compound of chica 3, Y, is O.
- The compound of claim 1, wherem R, oursprises a polyalbylene exide residue.
- The compound of claim 6, wherein R, comprises a polyethylore glycel residen.
- 8. The compound of slaim 3, wherein  $R_{\rm c}$  comprises a polyethylene glycel residue.
- The compound of claim 6, wherem R, is relected from the group consisting of (1-Y,)-(CH<sub>2</sub>)-O-(CH<sub>2</sub>CH<sub>2</sub>O),-A,
- -C(=Y,)-Y, (CH,)-O-(CH,CB,O),-A, -C(=Y,)-NR,-(CIL)-O-(CILCILO),-A
- (CR, R<sub>0</sub>), O (CH<sub>0</sub>), O (CH<sub>0</sub>CH<sub>0</sub>O), A,
- NR, (CH,), O (CH, CH, O), A,
- -C(+Y,)-(CH),-O-(CH,CH,O),-(CH),-C(-Y,)-.
- -C(-Y)-NR, -(CH,)-O-(CH,CH,O),-(CH,)-NR, -C(-Y)-,
- (CR<sub>2</sub>R<sub>2</sub>),-O(CII<sub>2</sub>)-O(CII<sub>4</sub>CH<sub>2</sub>O),-(CII<sub>3</sub>)-O(CR<sub>4</sub>R<sub>2</sub>),-, and
- · NR II (CH) A O (CH, CH, O), (CH, ) A NR o
  - whereto: Y, and Y, are independently O, S or NR,
- a is the degree of polymerization:  $R_{10}, R_{4}, \ \text{and} \ R_{10} \text{ resched}$  independently schooled from among H,  $C_{40}$  alkyla,  $C_{142} \text{ trunched alkyla}, \ C_{40} \text{ cyclosityla}, \ C_{40} \text{ investigated cyclosityla},$ myle, substituted aryle, arallyle, C, , beteroallyle, substituted C, betervallyle,
- C., alknowy, phenomy and C., heteroalkoxy; e and fare independently zero, one or erro; and
  - A is a capping group.
- 10. The compound of claim 9, wherein K<sub>1</sub> comprises 40-(CH<sub>2</sub>CH<sub>2</sub>O), and x is a positive integer so that the weight average molecular weight is at least about 20,000.

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-

11. The compound of claim 3, wherein  $R_{\rm i}$  has a weight average molecular weight of from about 20,000 to about 100,000.

- 12. The compound of claim 3, wherein  $R_{\rm s}$  has a weight average molecular weight of from about 25,000 to about 60,000.
- 13. A compound of alaise 3, conversions the forms

14. The compound of claim 13, wherein D. is

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15. The compound of claim 13, wherein D<sub>i</sub> is

The compound of claim 1, wherein I<sub>q</sub> is (CH<sub>2</sub>CH<sub>2</sub>O)<sub>2</sub>.

 The compound of claim 1, wherein L<sub>2</sub> is selected from the group consisting of -CH<sub>2</sub>, -CH(CH<sub>2</sub>), -CH<sub>2</sub>-C(O)NBCH(CH<sub>2</sub>), -(CH<sub>2</sub>), -CH<sub>2</sub>-C(O)NBCH<sub>2</sub>, -(CH<sub>2</sub>),-NH, -(CH<sub>2</sub>),-NH-C(O)CH<sub>3</sub>),-NH, and -CH<sub>2</sub>-C(O)NBCH(CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>).

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wherein  $R_1$  is a PEG residue and D is selected from the group consisting of

where it is a residue of an amina or a hydroxyl- containing drag.

- A compound of claim 18, wherein B is a residue of a member of the group compitting of: democrabicia, donorchicia; p-animouspilius mentard, molphalau, Ara-C (cyfunine mabinaside), leucme-Ara-C, and generinarios.
- 20. A method of creatment, comprising administering to a maximal in, need of such treatment an effective content of a compound of class  $I_s$  wherein  $D_s$  is a residue of a biologically active moiety.
- A method of presument, comprising administrating to a manuful in need of such greatment on effective amount of a compound of claim 15.

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22. The compound of chars 1, wherein Ar congress the formula:

where is R<sub>11</sub> and R<sub>14,20</sub> are individually selected from the group consisting of hydrogen, C<sub>14</sub> allyle, C<sub>12</sub> hemothed allyle, C<sub>2</sub>, cycleslight, C<sub>2</sub>, reluminated allyle, C<sub>2</sub>, a subministed cycleslight, aryle, assultationed myth, analysh, C<sub>12</sub> histocolilyts, subministed C<sub>14</sub> heterostryle, C<sub>24</sub> allowy, phenoxy and C<sub>14</sub> heteroskory.

23. The compound of chilm 22, wherein  $R_{\rm tr}$  and  $R_{\rm th,th}$  are each H or CH  $_{\rm p}$ 

24 A method of perpaining a polymer conjugate, comprising: reacting a compound of the formula (VIII):

wherein

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 $L_{\gamma}$  and  $L_{\alpha}$  are instrumentally schooled hides

Let us be a few definitions of the definition o alking, C., alkery, phenory and C., beterculkery;

At is a mosety which when included in Formula (I) forms a multi-inheritated aromatic hydrocarbon or a multi-subministed britaneyolis; group, and B', is a residue of a hydrocyl- or an unine-containing moiety;

with a compound of the formula (IX):

$$R_1 = \begin{pmatrix} R_1 \\ \vdots \\ R_N \end{pmatrix}_{m} \begin{pmatrix} M \end{pmatrix}_{n} \begin{pmatrix} Y_1 \\ \vdots \\ Y_N \end{pmatrix}_{m} \begin{pmatrix} G_1 \\ \vdots \\ G_N \end{pmatrix}$$





 $D_{\rm g}$  and  $D_{\rm d}$  are independently OH, a leaving group which is coparity an unprotected assists or hydroxyl or a terminal branching group;

R, is a polymeric maidus;

Y, is O, S or NR.

M ir O, S or NR; (a) is zero or era;

(m) is 0 or a positive transport

(n) and (p) are independently 0 or a positive integet;

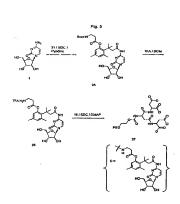
Yes are independently O, S or NR at and

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 $R_{\rm tot}$  are independently selected from the group constituting of hydropen,  $C_{\rm tot}$  alleyla,  $C_{\rm tot}$  browthed slityle,  $C_{\rm tot}$  events of slityle,  $C_{\rm tot}$  alleyla,  $C_{\rm tot}$  browthed slityle,  $C_{\rm tot}$  archivitated cycloslicyls, aryle, submitted style, archivitated  $C_{\rm tot}$  between  $C_{\rm tot}$  and  $C_{\rm tot}$  between  $C_{\rm tot}$  archivitated  $C_{\rm tot}$  between  $C_{\rm tot}$  and  $C_{\rm tot}$  archivitated  $C_{\rm tot}$  between  $C_{\rm tot}$  and  $C_{\rm tot}$  archivitated  $C_{\rm tot}$  between  $C_{\rm tot}$  and  $C_{\rm tot}$  archivitated  $C_{\rm tot}$  archivitated  $C_{\rm tot}$  archivitated  $C_{\rm tot}$  and  $C_{\rm tot}$  archivitated  $C_{\rm t$ alkyla,  $C_{14}$  allowy, phenoxy and  $C_{14}$  betrealkoxy; under conditions sufficient to cause a polymeric exclusion to be formed.

Fig. 2



# 【国際公開パンフレット (コレクトバージョン)】





No. Sq. 14. Rg = 50 sq. 18. Rg

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# TERMINALLY-BRANCHED POLYMERIC LINKERS AND POLYMERIC CONTIGATES CONTAINING THE SAME

#### PECHNICAL FIELD

The present invention relates to new types of stretinally-activated polymeric exact that which are useful in forming large acting conjugates of bioscieve materials. In particular, the invention solven to polymeric-beared conjugates having increased throughoutic polymeric and methods of preparing the same.

#### RACKGROUND OF THE INVENTION

- Over the years, several exclude of administering biologically-effective materials to natemath have been proposed. Many motivated agency are available as weits-calable with an ed-are beriched in phenomental formalisment rathartly easily. Problem state when the derived sweitshoal spent is either insoluble in squous failed or is repidly depended age. Administer after expectable (failed to suphable).
- One vary to wholdlist methods again in its include them to part of a subside proting. Proving private plantice detection review of a binding-land-part pour compand with, upon enginite reviews, everally liberan the private personal to the proving proving the part of the proving proving the proving prov
- Prodrugs are office blologically inen or enterentially functive furms of the parent
  or active compound. The rate of release of the entire drug, i.e., the rate of hydrolysis, is

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utilization by several factors but especially by the type of board joining the ported drug to the modifier. Care must be subset to world preparing products which are eliminated floorly the kidney or reductar condoderial systems, etc. before a sufficient emonate of hydrolytis of the percea compounds occurs.

Interpreting a physics are pair of a product prison has been suggested to become the circulate follow of a refug. However, the broom demonsted the states only one or any polyment of has been loow in 8,000 dathors under enceptantly to custom biologically parties arbitrates much as hillands compounds, the resulting configurate may paid of distriction to the compounds of the states or completely composed to the state of completely configurate are to produce of the first state conjugates are so productly districted from the body date event if a highly state parties are to produce control beginning to the completely configurate are to produce control beginning to configurate values of the produce reduction for encoding of support reduction for improvement of grants to the beginning and, not associated for agreement reduction or requested grants to the configuration of the configurati

Comptother: a end related biologically active analogs are often poorly water ablable and are examples of substances which would benefit from PEO produing technology. A brief overview of some previous work in the field is presented below.

Olays, et al., J. Bionetties, and Committed Polyments Vol. 19 Am., 1995, 51-66. disclose downshirts. PSG computes which are prepared by backing the tree substitutions: the various blacking circledding enters. The nelector's recipited of the PSG such however, is only about 5,000 at most. Thus, the in\_then horself are use fully vallaged becames the conjugates are substantially averaged agric to sufficient inlessing hydrodysis.

U.S., Pause No., 45A-377 destainer ceredo single 24003-mempeterios restrici sida sins in sida via frience se sere sida produje. The effective dos not, horrore, student using no union sed as part of a lichage visità novada startà the siduled se restricità più princiale vesigità projeme sodora Essema passino, e condenere ly riedesa producti in 1546 2 del 10-75 primes. Updrobjula in sulta Consepsative, il desa producti in 1546 2 del 10-75 primes. Updrobjula in sulta Consepsative, il del spicitory desimated from the body before a demanyori della della sinchia producrational sida della sida richiale sidad visiona della sida sida della sida della sida della sida della sida della sida richiale sidad sida sida della sida sida sida significanti sida della sida dell

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Commonly-assigned PCT publication WOS623794 describes bis-conjugates to which one equivalent of the hydroxyl-containing drup in statched to each terminal of the polymer. In spite of this solution, techniques which would further increase the payload of the polymer have been cought.

Thus, fizere continues to be a need to provide additional inclinelogies for ferming produces of therapeumic moieties such as completherm and related enalogs. The present invention addresses this need.

#### SUMMARY OF THE INVENTION

In one aspect of the invention, compounds of Formula (f) are provided:

(i)  $R_3 = \begin{pmatrix} R_2 \\ C \\ R_3 \end{pmatrix} \begin{pmatrix} M \\ C \\ R_3 \end{pmatrix} = \begin{pmatrix} K_2 \\ K_4 \\ K_5 \end{pmatrix} \begin{pmatrix} K_4 \\ K_5 \\ K_6 \end{pmatrix} = \begin{pmatrix} K_4 \\ K_5 \\ K_6 \end{pmatrix}$ 

R, is a polymeric residue; Y, is O, S or NR.;

M in O, S or NR<sub>si</sub>:
(u) is zuro or a positive integer, preferably 1 or 2;

(e) is zero or core;

are independently H. H. or

(n) and (p) are independently 0 or a positive integer;  $Y_{2,p} \mbox{ are independently O, S or NR}_{10}.$ 

R<sub>2-4</sub> are independently selected from the group consisting of hydrogen, C<sub>1-6</sub> alkyle, C<sub>2-6</sub> branched alkyla, C<sub>3-6</sub> cyclonikyla, C<sub>1-6</sub> autorizand alkyla, C<sub>2-6</sub> autorizand cyclonikyla, styla, substituted utyla, arabyta, C<sub>3-6</sub> beteroalkyla, substituted C<sub>3-6</sub> beteroa WYO 02/00006A

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slikyla,  $C_{i,i}$  alikuxy, plomoxy and  $C_{i,j}$  hostroellexxy;  $D_{i}$  and  $D_{i}$  are independently OH,

or additional branching groups described below.

Within formulae (IV) and (V), (v) and (i) are had

Within formulae (IV) and (V), (v) and (i) are independently 0 or a positive integer up to about 6 and preferably about 2;

Jia NR<sub>27</sub> or

L<sub>1</sub> and L<sub>2</sub> are undependently selected from the group consisting of O. S and MR<sub>+S</sub>

R<sub>11-11</sub> are independently selected from the group consisting of O. S and MR<sub>+S</sub>

C<sub>10</sub> alkyla, C<sub>10</sub> branched alkyla, C<sub>20</sub> eyeloalkyla, C<sub>20</sub> substituted alkyla, C<sub>40</sub> substituted

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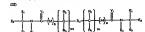
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cyclosikym, arys, substituted arys, araltys,  $C_{tot}$  bearcoalitym, substituted  $C_{tot}$  bearcoalitym,  $C_{tot}$  arbory, phenory and  $C_{tot}$  bear coalitons;

- At it a mainty which when included in Formula (I) forms a units cubstituted aromatic hydrocarbon or a multi-cubstituted betweeping group; and
- B<sub>1</sub> and B<sub>1</sub> are independently selected from the group consisting of leaving groups.
  Oh, residues of bytestayle or artise-tensishing moisties.
  - In one particularly preferred espect of the invention, the polymeric residue is also substituted on the distal portion with a mostery of florunin (II) below:



where all variables are an pervisently defined. Ellinencomal components are than formed when the polymeric resident (iv.) inhabites both an eliptic and are energis terminal likeling groups so that two, four: or come equivalents of biologically sortive agent, drong or protein, designated lateria in II, or II, on the followed: An example of south inflorational polymer transport from in bisturents thebre a formats (III):



For purposes of the present invention, the term "residue" shall be understood to russo that portion of a biologically socies compound which remains after the histogically active compound has enforgore a substitution reaction in which the produce cervices portion has been netteched.

For purposes of the protect invention, the term "elley" shall be understood to include straight, branched, substituted, e.g. halo-, alterny-, and nirro-,  $C_{\rm rel}$  slights,  $C_{\rm p,e}$  eyelously is or substituted cyclothy/s, etc.

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For purposes of the present invention, the term "substituted" shall be understood to believe adding or replacing once more steads occasioned within a functional group or compound with one or more different atoms.

For purpose to the greate invention, advanced delyte broke or investigable, intended or investigable, in intended problems of managemental post and managemental mentioned or problems in intended management on the 4 of delaways being broked management or in the first investigation of the state of the sta

The term "sufficient amounts" for purposes of the present invention thall teran an amount which otherws a therapastic effect as such effect is understood by those of ordinary skill in the art.

One of the chief desiration of the compounds of the present invention is that the desiration has not high provided power and opposition that previous excitorious. It is parently professed their the polytopiate of which only principle lands (Collection) their theoreties the violatedy lands (Collection) their provides principles in lands (provides and their provides) and provides of reservation inventional transition inventional provides (provides) and their provides (Collection) their provides (Collection) that their prov

Methods of making and using the compounds and conjugates described hertin are also provided.

### DRILP DESCRIPTION OF THE DRAWINGS

Figures 1- 5 schematically illustrate methods of forming compounds of the protein invention which are described in the Examples.

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#### DETAILED DESCRIPTION OF THE INVENTION

# A. FORMULA (I)

In one preferred embodiment of the invention, them are provided compounds of

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R, is a polymeric resident, Y, is O, S or NR<sub>2</sub>. M is O, S or NR<sub>6</sub>. (a) is zero or one;

(in) is sure or a positive integer;

\* - ( ) ( ) ( )

E,, are independently II, E, o

<del>([])</del> []—

(c) and (p) are independently 0 or a positive integer,  $Y_{b,i}$  are independently O, S or NR  $_{ini}$ 

R<sub>12</sub> are independently selected from the group consisting of hydrogen.
C<sub>n</sub> allylis, C<sub>n1</sub> bronched allylis, C<sub>n2</sub> cyclestrylis, C<sub>n2</sub> substituted allylis, C<sub>n3</sub> substituted cyclestrylis, argis, substituted cyclestrylis, argis, substituted cyclestrylis, argis, substituted C<sub>n2</sub> heterocklyris, substituted C<sub>n2</sub> heterocklyris, substituted C<sub>n3</sub> heterocklyris.

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D, and D, are independently OH.

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v) and (f) are independently 0 or z p

 $L_1$  and  $L_2$  are independently selected bifunctional links  $\pi$ 

1<sub>1</sub> and 1<sub>4</sub> are monepsendently asserted returned instant.

Y<sub>ab</sub> are independently selected from the group consisting of O, S and NR<sub>c</sub>c

R<sub>11-12</sub> are independently selected from the group consisting of Psychogen.

C<sub>bb</sub> slight, C<sub>11</sub> branched alloyis, C<sub>ab</sub> oychoolityis, C<sub>11</sub> substituted alloyis, C<sub>ab</sub> one-both

or slight, C<sub>11</sub> branched alloyis, C<sub>ab</sub> oychoolityis, C<sub>11</sub> substituted alloyis, C<sub>ab</sub> one-both

or slight, C<sub>11</sub> branched alloyis, C<sub>ab</sub> oychoolityis, C<sub>12</sub> substituted alloyis, C<sub>ab</sub> one-both

or slight, C<sub>11</sub> branched alloyis, C<sub>ab</sub> oychoolityis, C<sub>ab</sub> substituted alloyis, C<sub>ab</sub> one-both

or slight, C<sub>ab</sub> substituted alloyis, C<sub>ab</sub> oychoolityis, C<sub>ab</sub> substituted alloyis, C<sub>ab</sub> substituted allo oyelosikyla, aryk, substituted aryk, aralkyla,  $C_{\rm pe}$ beturosikyla, substituted  $C_{\rm tot}$  between slicyls, C14 slixxy, phenoxy and C14 beservativaxy;

Ar is a moisty which when included in Formula (i) forms a multi-substituted ne bydrocarbon or a multi-substituted heterocyclic group; and  $B_{\gamma}$  and  $B_{\gamma}$  are preferably independently selected from among leaving groups, OH, 11/O 62 OneOne

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residues of hydroxyl-containing moieties or residues of smins-containing maleties. In mother preferred embodiment,  $D_1$  and  $D_2$  are independently selected termini

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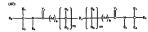
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 $E_{3,m}$  are as lected from the mand group which defines  $E_{1,c}$  above, except that wotin the definition,  $D_1$  and  $D_2$  are changed to  $D^1$ , and  $D_2$  which are defined below. Within this embodiment,  $D^1$ , and  $D^1$  can be independently OH, a mointy of formula (IV) or (V), or

where  $B_{i,m}$  are celested from the rane group which defines  $B_{i,m}$  except that which in the definition  $D_i$  and  $D_i$  are charged to  $D_i^*$  and  $D_i^*$  and  $D_i^*$  independently GH. Germin  $(D^i)$  or formula  $(V)^i$ . As one he approximated from the above, when the terminal branching is taken to in the limit entors with a bifuctional polymer  $B_i$ , up to skitces (16) equivalence of the i-can be becomed even the polymeric plants.

In those arpects of this embodizem where bis-substituted polymeric residues are dealered, some preferred polymeric transport systems of the invention are shown below as formula



wherein all variables are as proviously describ-

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The multi-loading polymer pranaport system of the present invantion is based in large part on the polymeric readuse designated berein as  $R_{\rm p}$ . Optionally,  $R_{\rm p}$  includes a complant group. The polymer suppling group A include, for example, modeless such as hydrogen,  $CO_{\rm p} | k_{\rm p} C_{\rm p} | k_{\rm p} |$  and of the models of the hydrogen,  $CO_{\rm p} | k_{\rm p} C_{\rm p} | k_{\rm p} |$  and of the models of the model of the polymeric constants of farmula (II) shown below, which

forms a bus-system: (II)

E, — (M) (R)

wherein all variables are as previously described. It will be understood and approxisted that the oralizable terminal branching described above applies equally in the bis-systems as well.

With regard to the other veriables which comprise the formulae of the present inversion, the following are preferred:

Y, are each oxygen,

 $R_{2\rightarrow}$  and  $R_{e2}$  are each preferably hydrogen or lower alkyl, e.g.  $C_{tai}$ 

 $R_{10}$ ,  $R_{10}$  and  $R_{10}$  are preferably -CH<sub>3</sub>; (m) in 1 or 2;

(n) and (p) are each either zero or as integer from 1-4;

(v) is zero or 1;

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(i) is 1;

1, is (CH\_CR,O),-; and

1, is one of CH<sub>2</sub>(x). (CH<sub>2</sub>)x, (CH<sub>3</sub>)x (CH<sub>3</sub>

CHIP-WIP CONDERCENT (CHIP-VIPCONCHIPMIP OF

#### B. DESCRIPTION OF THE APMOINTY

Referring to Formula (I), it can be seen that the As is a stockety, which when techniced in Formula (I), items a multi-substituted ecountric hydrocarbon or a studisubstituted betweepolite group. A key finance is that the Az moiety is geometric in antare.

substanted beterocyclic group. A key feature is that the Ar modely is arometic in enture.

Generally, to be aromatic, the n electrons must be absend within a "cloud" both above and below the plane of a cyclic molecule. Puriferment, the number of n electrons must satisfy

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the Rückel rule (4x+2). These of creamery skill will realize that a suyrised of mointies will trainful the arcumula requirement of the mointy and thus are quitable for use herein. One particularly preferred arcumula group is:

wherein  $R_{\infty,0}$  are selected from the same group which defines  $R_{\omega}$ . Alternative arounation groups include:

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externs to  $\Delta C_s$  and  $Z_s$  are independently CR<sub>p</sub> as  $100_{p}$ , and  $M_s$  a, 10,  $S_t$  are  $100_{p}$  when  $N_{tot}$  are actioned from the except gain as that which there  $S_t$  are  $T_t$  are consciously, and produced a contemporary  $T_t$ . However, of the first and this exceptional rings are also contemporary and  $T_t$  and a horner and obtaining veryidents and their include designates are also contemporary. In all in the temperature of the principal of the first arrangement of the second of the se

# C. <u>DRUG GENERATION YIA HYDROLXSIS OF THE PROBRUG</u> The prodrug coropounds of the greatest investion are designed so that the t<sub>id</sub> of

hydolysis in et. og. ellerinderine in jamene.

The lishage schoded in the etemposada have hyprivlysis ratus in the plasmo of the assemal being (reced-slight habout courgh to after auditions amongs of the parent conseponds, et., the slower of hyprograms of the parent compounds being in conseponds, et. the slower of hyprograms plasmons plasmons in the plasmons approximately to the consepond of the present beveration have a facilitation. Some performs compounds of the present beverate have a facilitation between the consepond of the present between the sense and the plasmons is desired to have referred to the consepondors have a plasmon in plasmon in the plasmons in death of 12 hour, Trainfords, the consepondors have a plasmon in plasmon in the plas

#### D. SUBSTANLIALLY NON-AMELGENIC POLYMERS

As usued above, R<sub>i</sub> is a water soluble polymeric residue which is preferably substantially son-artification and as a polymbic base evide (PAO) or ophyrhythese gircol (PEO). In preferent aspects of the invantation, R<sub>i</sub> fastin involudes the previous/americand capping group, durignated hereit. as A<sub>i</sub>, which allows a bifunctional or bis-polymer system

As at example, the FEG resides parties of the invegers compositions can be selected from the following nor-Harding Nat:

-C(-Y\_2)-(CH\_1)-C-(CH\_1CH\_2O)-A.

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 $<(e^{-}v_{\mu}^{\lambda}, v_{\gamma}^{\lambda}, (cii_{\mu})_{\mu}^{\lambda}, (cii_{\mu})_{\mu}^{\lambda}, A_{\gamma}^{\lambda}$   $<(e^{-}v_{\mu}^{\lambda})_{\nu}^{\lambda}, (cii_{\mu})_{\mu}^{\lambda}, A_{\gamma}^{\lambda}$   $<(e^{-}v_{\mu}^{\lambda})_{\nu}^{\lambda}, (cii_{\mu}^{\lambda})_{\nu}^{\lambda}, A_{\gamma}^{\lambda}, A_{\gamma}^{\lambda}$ 

16 wherein Y, and Y, are independently O, S or NR<sub>10</sub>;

s is the degrees of polymerization:  $\sum_{k \geq 0} R_{kk} = n^{2} R_{kk} = independently selected from smoog B. C_{r_{k}} alklyb, \\ C_{k+1} branched alklyds, C_{k_{k}} eyclocityds, C_{r_{k}} autonimmd alklyds, C_{k_{k}} abstaintand eyclosikyds, eyclys, authorizond eyclosikyds, eychystowd eych, astalyds, C_{k_{k}} betweellyds, substributed C_{r_{k}} betweellyds, exception of the property of the pro$ 

2.5 C<sub>6.0</sub> alknowy, phenomy and C<sub>1.0</sub> between knowy; e and f are independently zero, one or two; and

A is a capping group.

The degree of polymerrastion for the polymer (x) can be from about 10 to shoul

2.300. This represents the number of repending units as the polymer duties and is dependent on the anchoralize weight of the polymer. The (A) moiety is a coppring group as defined bretin, so a group which is found on the reminal of the polymer and, is some appearing, on the subsected from any of IL, NSI, OH, CO, N, Co, a Nije or other PECS seminal antesting proper, as eath proper is enderstood by those of ordinary Allia.

activiting groups, in a pain groups are cancermous by under our consulty statis.

Also useful are polytopolous glytosis, hemicabe PLG-derivatives such as these described in commonly-assigned U.S. Patent No. 5.44, 557, "Nat-PRI"s" and embisary PDG's such as flavor fearthead in Section 1901, "Nat-PRI"s" and embisity of Derivatives 1997-1991. The discharge of each of the foregoing is incomposed to

trytos Jerusaria 1997-1998 . Le siluciones e acus oi es acerganq o nompossado
bereis by reference. I will be suderestodo das the varse-solute portures ente
funcionalizad for attachment to the befunctional lichage prosps if required without undue
apprintentation.

bus further embodimant R, is optionally selected from smoney one or more of

decurus, polyrinyl alcohols, cartedystrate-based polyrams, hydroxygropylanthucryl-2.3 WY) 62:00000

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antide, polyalkylene unides, section copolymens thereof. See also commonly-entitied U.S. Parent No. 6,153,655, the controls of which are incorporated havein by reference.

- to amony aspects of the propent invention, jgg-softwated polyethylene glycols ere preferred when di-or more substituted polynon conjugates are dealerd. Alternatively, polyethylene glycols (PEGs), menu activated, Co. alcyl-terminated polyellylene exides (PAO's) such so more-methyl-terminated polyechylene glycols (mPEO's) are preferred when mono-substituted polynours are desired.
- In order to growide the desired by drolyzable biology, mono- or di-acid activated polymers such as PEG acids or PEG diacids can be used as well as mono- or di-PEG agrices and mono- or di-PEG drob. Suitable PAO soids can be synthesized by first converting mPEG-OM to an ethyl cater followed by superification. See also Gehrhardt, H., et al. Polymer Bulletin 18; 487 (1957) and Veroness. F.M., et al., J. Controlled. Release 10; 145 (1987). Alternatively, the PAO-acid can be synthesized by converting mPEG-OH cate a s-budyl enter followed by soid cleavage. See, for example, commonly assigned U.S. Peters No. 5,605,976. The disclosures of each of the foregoing are Incorporated by reference hereic.
- Although PAO's and PEO's om vary substantially to average molecular weight, the polymer parties of the prodrug is at least about 20,000 weight average in most aspects of the invention. Preferably, R, has a weight average melocular weight of from about 20,000 to about 100,000 and more preferably from about 25,000 to about 60,000. The everage molecular weight of the polymer selected for lociusion in the prodrog west bo sufficient so as to provide sufficient circulation of the product before bythrolysis of the
- The polymeric autorances ancluded herein are preferably water-soluble at rec temperature. A non-limiting list of such polymers include polyalitylene oxide homopolymers such as polyethylene glycol (PEG) or polypropylene glycols. polyexyethylenated polyels, copolymers thereof and block copolymers thereof, provided that the water solubility of the block copulymers is maintained. 30
  - As an alternative to PAO-based polyment, effectively non-antigosic materials such as dectum, polyvinyl alcohols, carbohydrate-based polymers, hydroxypeopylms/hacrylamide (HPMA), and copolymen thereof etc. and the like om be used if the same type of activation is employed as described horein for PAO's such as

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PECT. Those of ordinary skill in the sit will reake the disease gain gin is movely literatorize and first all polymeric unstraints having the qualities described berin are consemplated. For purposes of the prevent investion, "distorively reasonatingsid" and "voluntarially con-emigrate" shall be understood to include all polymeric nestraints and extension to ear as being subsensivity nestentiar used on clinities are represented and extension of the ordinary contractions.

It will be clear from the foregoing that other polyalitytene oxide derivatives of the foregoing, each as the polypropytene glycol needs, etc., as well as other bi-functional linking groups are also contemplated.

## 10 E. PRODRUG CANDIDATES

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#### 1. Resident of Hydraust-containing Occasionals

Countribusin and Rolated Tenoiroperson Libibition
Computation is a water-insoluble systems; a strate-in produced by Computation

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accessionate treas fredigenous to Chiru and neohyporthys facilité twee inférieuxes to helia. Camputification and rélated o-supervede and sealogs are alse Enerous to be proteins ministence or artitumes agents end have been above to exhibit these servivieis ju gings and <u>purity</u>. Camputificacio and related compounds are also candidates for convention to the orderings of the protest intervales.

Camptotherin and certain related analogues above the structure:

From this own structure, arrend borons coolings have been prepared. For all the properties of the properties of the properties of the same than the properties of the same than the properties of the  $\theta$ -positions with a sample of treatment  $C_{i,m}$  all prior  $C_{i,m}$  alloys or  $C_{i,m}$  alloys or  $C_{i,m}$  alloys or policeably bladed to the ring by a bettermining in  $C_{i,m}$  alloys or  $C_{i,m}$  and  $C_{i,m}$  alloys or  $C_{i,m}$  alloys or  $C_{i,m}$  alloys or  $C_{i,m}$  alloys or  $C_{i,m}$  all  $C_{i,m}$  all  $C_{i,m}$  and  $C_{i,m}$  all  $C_{i,m}$  all  $C_{i,m}$  all  $C_{i,m}$  and  $C_{i,m}$  all  $C_{i,m}$ 

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PCT/T/S02/04/180

carbazides, phonyl hydrazine derivatives, aratno-, aminoalkyl-, aralleyl, etc. Other substitutions are possible in the C, D and E rings. See, for example, U.S. Petent Nos. 5,004,758; 4,943,579; Re 32,518, the consents of which are incorporated hestin by reference. Such derivatives can be made using known synthetic techniques without endoc experimentation. Preferred samptotherein derivatives for our herem include those which metude a 20-OH or smother OH mucety which is capable of reserving directly with artivated forms of the polymer transport systems described herein or to the linking moiety intermediates, e.g. !minodiscette acad, etc., which are then associate a polymer such as PBG.

Reference to comprehenin malogs herein has been made for purposes of illustration and 10 not limitation.

b. Taxenes and Packtacel Derivatives One class of compounds included in the product compositions of the present invention is taxance. For purposes of the present invention, the term "taxanc" includes all compounds within the taxant family of temperate. Thus, taxof (pacificate), F-enbentured it is bettern carbony/-emits derivatives (saxutere) and the like as well at other analogs. 15 which are readily synthesized using attributed organic trobusques or ere available from commercial sources such as Sigma Chomical of St. Louis, Missouri are within the acope of the present invention. These derivatives have been found to be effective sorti-execut agents. Nurserous studies indicate that the agents have activity against several 20 malignancies. To date, their use has been severely limited by, among other things, their about stupply, poor water solubility and a tendency to cause hypersmultivity. It is to be upderstood that other texanes including the 7-scyl-carbamates and 7-cerbaranes disclosed in community assigned U.S. Patent Nes. 5.622,986 and 5,547,981 cm also be included in the prodrugs of the present invection. The contents of the foregoing U.S. patents are 25 incorporated berein by reference. Positional is a preferred terane c. Add tional Biologically-Active Majeties.

In addition to the foregoing molecules, the prodrug formulations of the present invention can be prepared using many other compounds. For example, biologically-active compounds such as bis-PEG conjugates derived from compounds such as

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gemeitabine:

pedephyllotoxia

trazoic-hasod antificagal agress such as fluormazole:

ar ciskophros:

or An-C:

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The parent composed selected for product from most not in streambility ware incashed, affecting the polymorbased garding of the present resourcine set emperation, with a since for selection packs rectangular than the composals include, for composals counties, composals composals counties, composals composals counties, composals composals counties, composals comp

The foregoing a literatures of the indepting the value coulders which are subbles for providing of the present restorate. In we the conformed them the indepting the present restorate is an excellent present to the river quality and the indepting of the indeptin

2. Rations of Amine-containts 1 Economials
Is some aspects of the inventor, B, or D, is a resident of an unine-containing
composed, as con-limiting list of each authorise composed include motions of organic
composated, orayone, proceius, polypeptides, etc. Organic composated include,
injuried, previous and an architectural composated including datacontaining, proceius,
and polyperiod in the composate of the composated including datacontaining, proceius and processing or composated includes, without
accordition, previous composated in the composate of the composated in the composate of the co

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ridand text incidential to supposed, e.g., generabilities, etc. Alternatively, it can be a recide of a surprocurring extrinsionator agent, alle explosionals, met-indicative, sealfungal such as system activities general extra processing of the supposed of the control services system activities general exaligation, formitte sparts, control agent, control services system activities general exaligation, formitte sparts, controllering sparts, and substantial experts, security agent, serviced agent, development of the state of the spart of the spart

vancounterfoliage sparts, etc.

In a purious expanse of the invention, the mobiles compilating everyward in a yintigenity series composed that in mobiles for medicinal or disquared toward in the recognition of medicinal expansed to series. The recognition of medicinal expansed to medicinal expansed to series and excellentarial individual expansed to the interest to excellent expansed to excellent expansed to expose described exposed which can be modified. These of demand and but the interest expansed expansed expansed expansed and the interest expansed expansion expa

information for offidoristivy after the product gystem relaxion and regimented the private comparation for the control of the

immer sell chemistry, e.g., by sta enzymetic reaction oraque to that cell. 3. Leaving Grocous

In those aspects where B, or B, is a leaving group, anisable leaving groups insisted, without lincine inos, moistics such as N-hydroxybeanstrandyl, halogen, N-bydroxyphatatizmidyl, p-nitrophemoxy, insistandyl, N-hydroxyphatatizmidyl, p-nitrophemoxy, insistandyl, N-hydroxymaccintmidyl, thindeddigivly thinde, or other and Leaving groups as will be appreced to those of ordinary

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skill. The synthesis resultors used and described herein will be understood by those of ordinary skill without undue experimentation.

For example, an acytaide intermediate of compared (i) can be reacted with a reactest such as 4-niverpheny) obliveriormans, discontinuity) actions (USC), use to confide in the confidence of the phenologies of the desired activated degrees we The activity acytities of the phenology multiple proton of the the confidence of the phenology of the proton of the phenology of the proton of the phenology of the pheno

p-hydroxylexuryl slocked or the permuseberuryl alreaded and the o-hydroxylexuryl abcohol or the o-uninobraryl skehol cur be extried out with, for example, this sold interface activated polymers, productoryly carbonate activated polymers, scelebrytic exid activated and the example of the script polymers, productoryly carbonate activated polymers, scelebrytic exid activated activated polymers, productors of the risk loss, the "activated form of the PEG

softwared polymers, encollecturely carbonate activated polymers, eachorytie enid activated polymers, blocked emilso used derivatives. Once in place, the "sectivated" form of the PEG perdung (or blocked proteing) is ready for conjugation with an emisso or hydroxylcomissing compound.

#### P. SYNTHESIS OF THE POLYMERIC PROBRING TRANSPORT SYSTEM Synthesis of representative polymer produces is set forth in the Examples.

Generally, however, in one preferred method of propering the product unaquest systems, the polymer enables is that sensited to the transiting general Represently, the folialisation of the molities of general Represently, the folialisation of the Thiff, compresses which may also include a bilinearisation general florescent polymer of instantions to the polymer, the polymeric residue containing the terminal breaches at restent with the Thiff.

as reacted with the drug-TML portion ander continuous sourcess to asset we seen product.

Attachment of the bifurnational spacer containing the TML Drug component to the polymer partiest is preferably carried out in the presence of a coupling agent. A necessary

The propriet process is the control of the control

Predephly the substituents are reacted in an inest solvent such as methylene chloride, objections, DMF or mixtures thereof. The reaction also preferably is conducted

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in the protection of a base, such as dimetaylantanopycisium, discopropylethylantate, pyridiar, prinkylamina, etc. to neutralize ony salda generated and at a temperature from 0°C up to about 2°C (rooms imperature). More particularly, one nethod of preparing a polymeric transport system inclu-

More particularly, one method of preparing a polymeric transport system include, reacting a compound of the formula (VIII):

wherein all variables are as previously defined and B', is a residue of a hydroxyl- or an amino-comtaining mainty; with a compound of the (crauda (UX):

(XX)

 $R_1 = \left\{\begin{array}{c} R_2 \\ R_3 \end{array}\right\}_{R_3} \left\{\begin{array}{c} M \\ n \end{array}\right\}_{R_3} \left\{\begin{array}{c} M \\ R_3 \end{array}\right\}_{R_3} \left\{\begin{array}{c} M \\ R_$ 

R<sub>c</sub> is a polymeric residuer, Y, is O, S or NR<sub>c</sub> (s) is zero or one; (so) is O or a positive integer, Y<sub>1</sub>, as independently electric for NR<sub>c</sub> is OB<sub>1</sub>, and NR<sub>c</sub> is OB<sub>2</sub>, and NR<sub>c</sub> WO #2066066

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E. are independently II, E, or wherein  $D_{\mu}$  and  $D_{\mu}$  are independently CH or a leavis reacting with an unprotected amine or hydroxyl or a terminal branching group;

(n) and (p) are independently 0 or a positive integer;

Y<sub>3.1</sub> are independently O, S or NR<sub>He</sub> and
R<sub>He</sub> are independently soluted from the group consisting of Σηδτορεία.
C<sub>1.6</sub> alkyts, C<sub>1.6</sub> transland alkyts, C<sub>3.6</sub> eyeloollyts, C<sub>4.6</sub> submitted alkyts, C<sub>3.6</sub> submitted cycloalkyls, aryla, substituted scyls, arelkyls,  $C_{p,k}$  heteroelkyls, substituted  $C_{p,k}$  between alkyls,  $C_{p,k}$  alkows, phenoxy and  $C_{p,k}$  heteroelluxy;

In further expects of the method,  $D_a$  and  $D_a$  are independently selected terminal branching groups of formula (X)

(×)

where  $E_{16,16}$  are selected from the error group which defines  $E_{2m}$  except that  $D_0$  and  $D_4$  are changed to  $D_1^i$  and  $D_4^i$  which are defined below. Within this embodiment,  $D_1^i$ , and D', on he independently OR, a melety of formula (IV) or (V), or (XI)

(XI)

wherein  $R_{high}$  are selected from the same group which defines  $R_{12}$ , except that D, and D, are changed to D\*, and D\*, which are defined as being independently OH or a having group which is expeble of reacting with an unprotested smins or hydroxyl.

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Such synthetic techniques allow up to nixteen (16) equivalents of carboxylic aci r activated carboxylic acid, for example, to be attached. As shown as the performed tructures beavin, FEO residues with terminally branched multi-acids are preferred expe-

Regardiess of the synthesis selected, some of the preferred compounds whi

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DOTAL PROPERTY.

wherein R<sub>i</sub> is a polymer residue such as a PAO or PEG end D is OH, formula (IV) or (V)

"iki. "iki.

W10 +1+V4+

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are B is a residue of an amine or a hydrocyt- containing freq.

In another preferred aspect of the invention, the compounds of the present

invention are of formula (XII):

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wherein all variables are as previously defined above.

#### G. RYPTIO DIAGNOSTICS

A further apport of the investme provides the origination of the investme probability prompts of the diagonates of sized to the transport admissional wherein the tag is selected for diagonate or managing prompts. Thus, a subsidied text proposed by building any minital asserting, then, a makes select reading, now pre-instantial critical persper, polio-populs such reagents reasonate balls, or other amenditude transport and prompts of the selection of the selection of the selection of the critical proper, polio-populs such reagents reasonate balls, or other amenditudes to the selection of the critical properties of the selection of a selection of the selection of the selection of a selection of the selection of the selection of the selection of a selection of the selection of a selection of the selection of the selection of a selection of a selection of a selection of a selection of the selection of a selection of a

In a still farcher spect of the invention, the invention tegral energisters are reliefly prepared, by prisones cantidod, who cynthis helds, facility prepared, by previous cantidod, who cynthis helds, selling facility and the control of the contro

Readly, for materiated leading of the reliance is a policie, the redupter say in plantament or a partiest or existent supports of the rings, a tumor. After multiferint time to allow the school contractopholish time benefits as the tumor strick, the signal presented by the label is demostly, for instrument, when they be yet redupted, comparisoned measured temporary for the production of the indiscenter in the yet parties measured derives such as a pursue source, or any other schools of the indiscenter in the yet parties measured derives such as a pursue source, or any other schools of the indiscenter of the school of the indiscenter of the schools of the indiscenter of the schools of the indiscent of the schools of the indiscent of the schools of the indiscent of the school of the indiscent of the schools of the indiscent of the school of the indiscent o

The detected signal is then converted to an image or anatomical analyse physicological determination of the tunner site. The image makes is possible to locate the tunner in vivo and to devise an appropriate thempositic strategy. To those embodiments

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where the tagged molecy is inself o therepestic agents, the detected signal provides evidence of austomical localization during treatment, providing a baseline for follow-up diagnosais and therepestic interventions.

#### FL METHODS OF TREATMENT

Author sepect of the pressed invention provides untilable of restremen for writen includal conditions in mannesis. The motivals behave destinisherating no the reasonate in noted of such treatment, an efficient natural of syndring, such as a small shoolf Ana-C-Pills conjugates, which has been present of streathed heren. The compositions are would face, tempor destings noted in produced destinates, relativity internal to prevending unstated of nephanes and preventing recurrences of neurotherophetic growthe in amounts.

The reasons of the profits a planticitients of the profit upon the power subscoled trainfold offerior. Committee, the reasons of profits upon the first trainfold offerior. Committee in the size of the size of

pharmaconical companions for distribution to assume. The pharmaconical companions are to distribution to assume. The pharmaconical companions are to the form of  $\sigma$  is likely assumed. The pharmaconical parameters of the form of  $\sigma$  is likely assumed to the contragation of the pharmaconical contragation of the companion of the contragation by my per form particular, as afteriors where the places in our following of the contragation by my per forms patched, e.g., by interespons, international, subdential interesting of the contragation of the form of the contragation of the contra

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Such administration may also be by influsion into a body space or carrity, as well as by inhabition and/or intransacl restes. In preferred aspects of the invention, however, the prodrugs are percentently administrated to measurable in most thereof.

#### 1. EXAMPLES

- The following examples arms to provide further approxisation of the invention but are not uneast in any way to rearried the effective scape of the invention. The underlined mit bold-fixed numbers recined in the Examples correspond to those shown in Figures 3-6.
- General. All rendriess when you whom to an annuadrant of day simming on magain Commentain impairs were used without furning refindation. All TFGO composeds were offered used revenues on the passenged distillance floateurs plant to the art. High errors were obtained with a TFGO. TF Med. System RNM CREATO instrument somet controllaborations as solvious also reported. NF CNMS control was controlled to the art of the a
- equivient (double mount of the C (5'VC).

  HEM. MEMOLAL Analysis (15'VC) were performed using a CS revented pines enform

  Goethers, direption (5'VC) were performed using a CS revented pines enform

  Goethers, direption (so dec incorric confidence with an 10'CD addust (4'VO) of

  missace-server are which pines. The abusiness were received as 25'de analysis of

  direction. To detent the pressure of any few 15'D and don to enform the presence of

  HEMLOGENET (20'VC), we require this plane storing dense and 25'de analysis. All the

  \$5'D (Originess Laborations), was employed. Boost do LECO and 10'V emblys, all the

  \$5'D (10'VC) and 10'VC analysis. The abusiness of any other performance of the analysis of the abusiness of
- 25 Bini Fi/Oyouday Orobota www Ers of Innii vol vap and was a 59% per by BFFC.
  Anthysis of Arthe Cicasinet in EEE Entherstrees. For all the electrations of an exercise in FEG determine, N-easyloyised new send as a model. The UV denotember of N-easyloyised new (IV) exemply define in IQI (IV) exemented as 227 first in the different concentration as 25 first in the different concentration as 128 first in the different concentration as 128 first in the different concentration to the NAM or construction. Or all southern the content plant of the devictions or a concentration that despite or concentration was administrated to be NAM.
- (O.D. at 257 nm for 1 mg/mL with 1.0 cm light path). PEGyluted and C derivatives were

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desired in EU/O in apprenium concession of 0.015 monibul, deved on 8 MV of 10 ha) and the UV observation of these consequent at 17th over whem the 15th of 10 ha) and the UV observation of 10 has one of 10 has one

PSSTEATED melphales derivatives were dissolved in DMP-II/O (St.) who is an approximate concentration of 0.011 pseudost. (Based on a 16% of 4.0 %), and the UV shouthouse of these composeds is 7.00 m was observabled. Using this whose and critiquing the shoutprion confidents, a channel dress the shows, the concentration of could be a supply used and country. Dividing this whose is the same concentration of could be a long to the same place and country. Dividing the value by the sample concentration of the same place and the same place the same place

grovided the percentage of mulpitalus in the sample.

Abbraviations. DCM (dichlormenthate), DMAP (4-dimenthylamino)pyridne), EDC (1-edv)-1-G-dimethylaminopropylyam-baliminie), ROBT (1-bydroxyberronviazole), PA (2-propose), NoMd (A-castlylompholius), TFA (strillowrascetie acid).

Exemple 1.

Compressed Se. A minister of emc (1), 179 g. 712 exectly, 3 or (100 erg, 1.78 mem), 1007 (6) Seg. 7, 178 mem), and IDCHIC (1) Seg. 7, 142 mem), 142 mem), 163 mem), or IDCHIC (1) Seg. 7, 142 mem), 164 mem), 164 mem), 165 mem)

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132.52, 133.54, 116.73, 138.22, 146.57, 149.90, 155.63, 155.96, 162.04, 171.89, 174.06. Krampik 2.

Composed 3b. Composed I via cospele visit. 2b using a sensitive contribute at the Dossigle I to produce 2b on 54% yield: "PC 1988 6, 1723, 1792, 1813, 2549, 2813, 131, 1313, 1319, 2344, 3922, 4049, 5018, 1922, 6172, 7438, 7494, 811, 1011, 1013, 1545, 1329, 1861, 1861, 1862, 11225, 11267, 1299, 1296, 1136, 1136, 11222, 1364, 1373, 13122, 1466, 1463, 1469, 1925, 1156, 1156, 1713, 1713, 1713, 1713, 1714, 1714

Example 3. Compound 4.c. Costpound 3.e (Child step 1.00 mmm) two stimed in ehybrion DCN (6 mills red TAA (4 mill) a room marginerium for 2.6 ii. Birlyi older was olderful the solution in projects the order product state of the colder product of the colder product state of the colder product of the colder pr

(d, /= 8.1, 13-5), 8.67 (ds, 14, 176); "C (yar (dmso-4) & 15.45, 19.67, 24.97, 31.05, 31.23, 38.56, 40.41, 48.53, 48.02, 61.02, 64.94, 74.64, 76.14, 33.74, 58.95, 94.32, 122.32, 132.41, 134.01, 135.67, 138.09, 146.71, 149.26, 164.50, 158.21, 158.72, 162.02, 169.65, 131.47.

Composer 40. Corposed 30 was religiented to the same condition as in Enumple 3 to
give to be EX's yield: "ILNORE (ONSO-4) 8, 1.32 (c. 18), (C.H.), (C.

Example 5.

Compound 6a. A mixture of PEG-arpartic acid (mw. 40,000, 5, 3 g. 0.074 mmol), 40

(385.6 stg. 0.74 rowol), NNAN (246 mg. 2.38 cmnol), HOSF (120.5 mg. 0.87 mmol), and

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EDC-RG (224.4 ng. 1.19 cm/s)) a mbyloso (DCM (6 md.) w s simile at 0 ° U for 20 md.). The residence was allowed to waste norm ampearment of according for 3 days and Blanch. The Elbest was accordinated in the case and the residen proprietables from 12 Me jor 2.7 g (200%) of product. The seminori state is the product assessed by UV surps was 211 write. ° US-NSE 8.14.04, 19-22, 20.65. 311.7, 13.3, 15.90, 47.8, 4.6.0, 47.8, 47

Exempts 6.

Composed 6. Composed 60-van religions for the wave combiners as in Exempts 2 to give 6b in ERN yield. The invasur of ear-C1 in the product maximum by IVV easily was 164-vel; "V: NORE 81-1312, 16:20, 24-02, 24-70, 34-70, 34-70, 11.5, 78-60, 78-60, 48-70, 48

Example 7. Ottopessed 9. FEGI deal (7, 15 g. 138 mans) was avenlesped on inductor over a 2 hour period followed by reserved 250 feet. At others they strong respect to 150 mans of 250 mil. At others they strong respect to 150 mil. The solution was cooked or 2.07 cet of replacement (246 g. 2.13) respective such as walled followed 150 million 150 million

"C NMR & 123.62, 128.10, 134.55, 152.00, 160.00.

Example 8.

PEG-cno-Aup-0-6-Bt (13). Compound 9 (sov. 40,000, 20 g. 0,459 mend) and separation and 6 -buyl one: MC3 (16, 1.0 g. 1.25 mazo) were disorded in adoptives DCM, 560med by self-disor of DNAP, 06,002 g. 3.55 mend). The solution was refluent oversight Solomout by recipions they define of skilly short (1.15 me held was oversight Solomout by recipions they define of skilly short (1.15 me held was

isolated by filtration and conventificed from PA (i.l.) twice. The filter cake was washed 31

methylms chiende-ethyl other (1100 mL, 8.2, wv) to give the product (50.9 g. 92%):

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(CH,CO,C(CH,)), \$2,007 (CHCO,C(CH,)), 155.924 (OCH,CH,OC(-C)NR), 169.674 (CH,CO,C(CH,)), 169.60 (CHCO,C(CH)), ). Example 9. PEG-crac-Asp-OB (12). Compound 11 (15 g. 0.725 mmm) was dissolved in DCM (150

mi.) followed by the solition of TFA (75 ml.). The relation was stirred at room temperature for 2 from one flatting (500 ml.) added to precipine the solid. The solid was instituted with houses to instruct of Arthoused by recognitization from difficult DCM of the control of the solid was refusioned in DCM (500 ml.), and washed with water (150 ml.). The organic layer was argument, detel over mileptown MpSO<sub>1</sub>, exceptionally one operation of the control o

1°C NAR 8 36.41 (СТСЯ,СОД, 59.177 (СВСИ), 64.390 (ССП,СТЬ,СОС-О)ЛП), 25 81.337 (СП,СО,ССС)Д), 32.697 (СПСО,ССПД), 156.172 (ОСВ,СТЬ,ОС-О)МВ), 17.1544 (СЭ,СО,ССПД), 172.211 (СВСО,ССПД), Example 10.

Best-Ag-Ag-Older (II), EDC-HCI (Aff. p. 124 Semily) was solid for a situation of Book's experiment of (L. p. 1, p. 4 Semily), aparties with design on the Old (p. 1, p. 2). Semily aparties with design on the Old (p. 1, p. 2) and old (p. 1, p. 2). Semily aparties with design of the Old (p. 2, p. 2). The existence was experiment of the might be some upon to promise processing and aparties was experimentally. Indirectly some of the experiment processing and experimentally. Indirectly some of the experimental processing of the old (p. 2, p. 2, p. 2), and (p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2), and (p. 2, p. 2, p. 2), and (p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2), and (p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2), and (p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2, p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2, p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2, p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2, p. 2, p. 2, p. 2). Semily (p. 2, p. 2, p. 2, p. 2, p. 2, p. 2

Example 11.

App.que-pt-04 (4) G. Compound 15 (3,0 g. 3,35 mont) was disorbed in DCM (39 mL) and TFA (15 mL) and the solution was size of fix 1 be recens taggement. The orbital was recorded or source and orbital solution was recorded or source and orbital solution was fixed DCM-64 orbital orbital product (1.14 g. 37%) as a white policie. "CVDAGR 33.52, 4.61%, 5.01.5, 1.90, 51.9%, 52.65, 11.92, 11.93, 11.94.1, 11.94.1, 11.94.1, 11.94.1

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#### Example 1

PEC-ER-Alp-A-p-C004 (TP. DMAY (cf. p. 2.56 meng) was added as a soliton of the end policy of the amount of the end policy of the end polic

Asample 13.

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30

Antergrat List.
PEG-cereschip-Aug-OH (E), Compound IV (E) g. 126 march and LiGH-IQ-OB g.
II 3 zerol) were disorded in 300 mL of water and the saladium circle ceresigia a reven
suspenzar. The 311 of the shakes was subjected to 2.15 per disorded to 141 per dis15 selson was extensed with DCM (F) of 500 mL), she regards byte secondard, shad ever
subplows MROO, and constrained with news. The reventer uncomplished from DCM
of their tig jet with product which was collected by Emotion and shed at 40° Commight to
pack 16 g/cMy of the encodes of 2000 CE(OR) 21.31 27.07.115.115.115.146.116.
220 (C) 1164, 71.445.74.211 (F) (D), 139.77.717.217.17.17.1746.116.174.116.176.646.

Met-OMe (19), Mchipalan (19, 130 g 3.18 mm) was suspended in 2,2 dismolocypropent (6.57 mil., 133.48 mm). To the supersion was added approach (6.4% %, 1.28 m.), and have been chanced (m.). The miniture was version to mill reflux with vigorous storring until solution started to ten shightly brown, Sollowed by shiring at recontemperature for 18 hours. The resistion infature was uncorrected in worse and the crude prodote proception forms the resistion miniture was uncorrected in worse and the crude prodote proceptions from the resident with the 2.0% and 18.0% when which we

protein precipitated from the resident with other. The solid was filtered, weaked was storp, and pushfield by Sillion gall ovicems chemisanography (CDC); 1 MeGLE = 9-5, 479 to yield the discord protein (IO-7<sub>26</sub> er<sup>2</sup>19); "C NoRIG 8 97-51, 403-40, 51.912, 53-455, 53.503, 172.1244, 126-976, 130-020, 149-033, 173-754.

Hero TML19-MH-OMe (33). EDC (0.52 g. 2.70 runol) and DMAF (0.988 g. 8.10 runol) were added to a mixture of 21 (0.53) g. 8.35 runol) and 20 (0.863 g. 2.70 runol) in

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mingrimes DDA (10 mil.) and mingrimes DDA (20 mil.) and "C im in its leith." The continum nature was entered on some appearant recording most artiforage the contentment of some DDA (10 mil.) and the DDA (10 mil.) and where the present via 10 mil. In 1817. The regions have we shall once an inhalpset assessment millio, concentration, and purified by Min and color and inhalpset assessment millio, and content of the proper of the color and the color and the 10 mil. 20 mil. 20 mil. 10 mil. 10 million (10 million 10 millio

10 Kangipi 1-h.
Yangipi 1-h.
Yangipi 1-h.
Yallap-Mei-Oblu TPA Sait (23). Compared 22 (0.737 g. 1.09 mostly was saired in DCM (yts.), and TPA (25 ml.) at most interparature for 2 hours. The reaction relation was concentrated, relationsheed in minimal DCM, and precipitated with relate. The protection

was concentration, reconstruction and assume assume assume (0.222, 3.79 %); "C FMSE
15 (CDC<sub>3</sub> + CD<sub>2</sub>O<sub>3</sub>O)) \$ 2,002 6, 25, 164, 31, 739, 31, 802, 3,527, 36,72, 39, 164, 40,340,
47,066, 2,2219, 53,306, 112,075, 123,206, 124,716, 130,377, 123,076, 133,180, 156,815,
133,194, 145,110, 149,250, 171,060, 174,1619, 172,650.

Example 17.
FEG-men-TM-Lip-Mid-Oble CD0. A rathase of FEG-ora-Aup-Aup-CHI (18, 1.6):
20. (19)1 (assys), 31 (1977), 2.9 (1976), 32 (1976), 4.9 (1976),

135.804, 137.737, 144.316, 149.063, 160.432, 170.602, 171.598.
Example 18.
Boe-173GLB-AraC (25). A solution of Ara-C (1, 9.88 g. 40.66 remail) in subydrous
yyndiac (33 mL) was odded to a relature of 23 (4.0 g. 10.17 armed), MOHT (2.49 g. 40.66

mmol), EDC (15.61 g, 81.12 mmol), and NbON (8.93mt., 8.21 g, 81.32mmol, 8eq) in anhydrous pyridine (200 ml.). The reaction mixture was stirred for 48 hours at 40 °C

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solve allogone, followed by conscrivation in solve. The entitle was redistributed in CLM (1997 m.), when there since when var (1997 m.) and release with SMIR (1998 m.). The expent keye was delet over comparison arthm, concernment, end predictely allowed to comparison produces, advantagely (2012—1, 2019 f.), why just that the destrolegebode (1.0.6 g. 37 % 19.7 % 19.7 % 19.5 % 19.7 % 19

TML4.AveC TTA. not 1(Q). Composed 30 (Q. 4.50 mml) was dissubside in TM-115 in all). Billion 40 billion 40 TM, 2003, pt. no. \*\*C. Reside in their war said red 0.7 or for 1.3 hours and concentrated in section is a cost to that, Brazillon was prosphered with DCA-drawled to point for the cost of LTQ, 7.7 (N). \*\*C. POSIG CTQ.\*\*, \*\*D.\*\*, \*\*I. POSIG CTQ.\*\*, \*\*D.\*\*, \*\*I. POSIG CTQ.\*\*, \*\*P. POSIG C

PEG-enc-Asp-Asp-TML: | B-Ara C, octamer (27). Compounds 26 and 18 were subjected to the same condition as in Example 18 to prepare 27.

Example 21.

20 In vitro and in vivo data for compounds 60 and 6h.

25

is this Exemple, in vivo and in vitro data are presented and compared to unmodified Ara-C. In Vivo

Adjustic souls mice were implained individually and only time frequence of 1.7.3.

On the other date of the control. The times to work in an observed meying work workly and measured done playable. The times were large to the other control are a determined by measured to one distriction of the other control and the other control

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nd, per morais. Catapounds were green looks in equal mole basis (shiebher amount of a work) or 150 mg/s) and of the other district pools of 150 (looks.) One of the other for a fine of the other shiebher (below). Musus weight and man the vero measured at the political per of ship of river weight from glow of 2. Days (effectiveness with determined by mangating amount goods in tended veros memoral (so weight) means of size. Per 20, 10) were used to the comparison of the comparis

Composed the demonstrated better entities as activity then neither Ant-C at only, 20% of the active perus compound about. Compound to a ston demonstrated significant officers, 13 Allough the WTCP was about twice of that which was revented the 6th, in norefaciless compound vary freezably assisted author. And, c. specially considering that the invention or approach or any fives a neithy 20% of the entire presentally considering that the invention or approach was for the 20% of the entire presentally considering that the invention or approach as the 20% of the entire presentally considering that the invention or approach as the 20% of the entire presental compounds down.

	Септровид	An (h)*	ICm (nM)*	LX-I %T/C*
20	Ara-C		10	74.0 (100 mg / kg)
	Compressed for	2.1	123	122 (20 mg /kg)
	Crespound 6b	53	958	59.3 (20 mg/kg)

All experiments were done at 37 °C in duplicate and I<sub>s0</sub> was measured by the disappearance of PRO derivatives. Standard deviation of measurements = a 10 %.
\* Norm baseline number volume was 1000 mm².

IN VETRO BLOASSAY

A series of in vitro sarys were conduced to determine the IC, for omnodified AAS-C and compound 10 using the 7355/O (motion lymphotic developers, Stochers Research Lambius, of liber. The 7350-0 cits were grown in 1920 I 1640 motion (Whichias Dioprodicts, Walkars Villa, Naryhand) - 1915 788 (Dychoe hos, Logan IV)-Biossays were preferred in flat reproduct motion considera sub-loss and fungitions.

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Are-C was discoved in DMSO and diffused to the appropriate concentration to culture media. The PEG-Ars-C compounds were dissolved to water and diffused to the appropriate concentrations in earlier media.

- The sexpy some performed to displace in New-Cell microtics cell colores place. The time of the serial distribution of the compounds were disms in the neutronic place. Calls were descholed by instability with 0.1 htt Tryptain "Versone 0.3". Tryptain was justified to by adding the appropriate model for each cell line containing 10% FSR. To creat well of the scientistic places, 10,000 cells have added 0.0. And tiger drop, and growth was measured by addition of a methodic findinger dys., Almans Blate, exceeding to the manufacturer acressed TSR. The contraction of the contrac
- intercurine places, 10,000 cells were abdob. After three thys, cell growth was measured addition of a metabolic indicator the, Ashare Bles, exceeding to be establishment? 10 protocol. This IC<sub>10</sub> value for the test companied and reference compound are provided above on the Table.

  While three have been discribed what are presently believed to be the preferred
- embodiments of the inversion, these skilled is the set will realize that changes and modifications may be made without departing from the spirit of the inversion. It is interned to obtain AU such changes and modifications as full within the true scope of the invention.

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### WHAT IN CLAIMED IS:

t. A compound comprising the form

R, is a polymeric resid Y, is O, S or NR.

M is O. S or NR,

E<sub>3-4</sub> are independently H, E, or

(a) is zero or nee; (m) is zero or a positive imager;

(a) sad (p) are independently 0 or a positive integer;

 $Y_{3\nu}$  are independently O, S or NR  $_{ee}$ 

A), we inequalizately selected from the group consisting of hydrogen,  $C_{i+}$  ollyist,  $C_{i+}$  transited allysts,  $C_{i+}$  optionityis,  $C_{i+}$  outstituted allysts,  $C_{i+}$  outstituted allysts,  $C_{i+}$  outstituted allysts,  $C_{i+}$  outstituted allysts, optionityis, option elicyle, C14 alkney, phrnoxy and C14 heteroalkoxy;

D, and D, are independently OH.

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or a terminal branching group;

wherein (v) and (t) are independ

 $L_{\rm i}$  and  $L_{\rm i}$  are independently selected bifurctional blakers;  $Y_{\rm int} \, {\rm are} \, \, {\rm independently} \, \, {\rm selected} \, \, {\rm from the} \, \, {\rm group \, consisting} \, \, {\rm of} \, O_{\rm i} \, S \, \, {\rm and} \, \, NR_{\rm jet}$  $\mathbf{E}_{\mathrm{OM}}$  are independently selected from the group consisting of hydrogen,  $\mathbf{C}_{\mathrm{OM}}$ 

alicyls, C<sub>340</sub> beautobad o'ltyls, C<sub>34</sub> cychoallyls, C<sub>14</sub> subminued alicyls, C<sub>34</sub> subminued o'yesseltyls, myls, subminued crys, aralicyls, C<sub>34</sub> subminued C<sub>14</sub> betereally)s. C., alkney, phenoxy and C, a betereology:

Ar is a molety which when included to Forenils (I) forens a multi-substitute mis hydrocarbon or a multi-substituted heterocyclic group; N<sub>c</sub> and D<sub>c</sub> are independently selected from the group constring of leaving groups, OB, residues of hydroxyl-containing moleties or amize-containing moleties.

The compound of claim 1, wherein R<sub>s</sub> further comprises a capping group A, selected from the group consisting of hydroges, NR<sub>p</sub>, OB, CO<sub>2</sub>H, C<sub>14</sub> moleties and



(c) and (p) we independently 0 or a positive integer;

V<sub>3,3</sub> are independently O, 5 or NR<sub>m</sub>;

R<sub>m</sub>, are independently nelected from the group constituting of hydrogen,

C<sub>1,4</sub> MD(s, C<sub>1,4</sub> Hornbod MD/s, C<sub>1,4</sub> Constituting, G, archivatored allysis, C<sub>1,4</sub> medical model of polytogen,

cyclosikytis, syste, nelectated styris, enables, C<sub>2,4</sub> betweenfoyte, substituted G<sub>1,4</sub> interespectively.

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alkyla,  $C_{14}$  alkoxy, phenoxy and  $C_{14}$  between theory:  $D'_{1}$  and  $D'_{2}$  are independently OR.

ł., ł.,

wherein (v) and (i) are independently 0 or a positive integer up to shoot 4;

i., and 1, are independently askeded bifunctional littlers,

V. are independently askeded to his flow gas up commissing of 0,0 3 and 700...

(ii), are independently askeded from the group consulting of 15 printing.

C., allotin. C., j. internal dedyth. C., architect. 6, r., instrinted shifts, C., anisottionally optionally, targin. arbitict. 6, internal configuration of the control of the co

At is a mosety which when included in Formula (i) forms a multi-substituted

arornatic hydrocurbon or a punkti-substruted hestrocycho group;

B, and B, are independently selected from the group consisting of having groups, OH, residues of hydroxyl-containing moistness or anning-containing mainties;

$$E_{e^{ij}}$$
  $-\left(\stackrel{\circ}{\xi}\right)\stackrel{\circ}{\xi}$   $-\sigma$ ,

D", and D", are independently OF

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- 5. The compound of claim 3, Y, is O.
- 6. The comprume of claim 1, wherein R, comprises a polyalitylene oxide residue.
- The compound of claim 6, wherein R<sub>1</sub> occuprises a polyethylene glycal residue.
- 8. The compound of claim 3, wherein  $R_{\rm g}$  coroprates a polyethylene given insidus.
- The compound of claim 6, wherein R<sub>1</sub> is selected from the group consisting of </pr
- (CR<sub>2</sub>R<sub>2</sub>), O (CH<sub>2</sub>), O (CH<sub>2</sub>CH<sub>2</sub>O), A, NR<sub>0</sub> (CH<sub>2</sub>), O (CH<sub>2</sub>), O (CH<sub>2</sub>CH<sub>2</sub>O), A
- -C(~Y\_)-NR<sub>23</sub>-(CH<sub>2</sub>)<sub>2</sub>-O-(CH<sub>2</sub>CH<sub>3</sub>O), -(CH<sub>2</sub>)<sub>2</sub>-NR<sub>23</sub>-C(\*Y<sub>2</sub>)-, -(CR<sub>22</sub>R<sub>23</sub>)<sub>4</sub>-O-(CH<sub>2</sub>)<sub>2</sub>-O-(CH<sub>2</sub>CH<sub>3</sub>O), -(CH<sub>2</sub>)<sub>2</sub>-O-(CR<sub>22</sub>R<sub>23</sub>)<sub>2</sub>-, sud
- ·NR<sub>30</sub>-(CH<sub>3</sub>)<sub>2</sub>-O-(CH<sub>2</sub>CH<sub>2</sub>O)<sub>2</sub>-(CH<sub>3</sub>)<sub>2</sub>-NR<sub>30</sub>wherein Y<sub>2</sub> and Y<sub>3</sub> one independently O, S or NR<sub>10</sub>:
  - x is the degree of polymentaction;

    R<sub>D</sub>, R<sub>D</sub>, and R<sub>D</sub> are independently selected from among H, C<sub>be</sub> slight,
- ng. c<sub>1,0</sub> are a composition of a meeting of a constituted silvia, C<sub>1,4</sub> aubstituted eyeloxikyia, α-yia, substituted aryia, critickia, C<sub>1,4</sub> aubstituted silvia, C<sub>1,4</sub> aubstituted eyeloxikyia, α-yia, substituted aryia, critickia, C<sub>1,4</sub> absterosibyia, substituted C<sub>1,4</sub> between thyta, C<sub>1,4</sub> alkary, phenoxy and C<sub>1,4</sub> between ilivoxy;
  - e and fare todependently zero, one or two, and
- A is a capping group.
- The compound of claim 9, wherem R<sub>1</sub> communes -O-(CH<sub>2</sub>CH<sub>2</sub>O), and x is a
  profitive integer so that the weight average molecular weight is at least about 20,000.

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- The compound of claim 3, wherein R<sub>1</sub> has a weight average molecular weight of from about 20,000 to about 100,000.
- The compound of claim 3, wherein R, has a weight average molecular weight of from about 25,000 to about 60,000.
- 13. A permensual of claims 3, communisters the forms

14 The compound of claim 13, wherein D,

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15. The compound of claim 13, wherein  $\mathbf{D}_i$  is

- 16. The compound of chaim 1, wherein L, is (CH<sub>2</sub>CH<sub>2</sub>O)<sub>2</sub>-
- 17. The compound of claims 1, wherein L<sub>2</sub> is salected from the group consisting of CH<sub>2</sub>, CH(CH<sub>2</sub>), CH<sub>2</sub>C(O)NHCR(CH<sub>2</sub>), (CH<sub>2</sub>), CH<sub>3</sub>C(O)NHCH(CH<sub>2</sub>, (CH<sub>3</sub>), NH-, (CH<sub>3</sub>), NH-CH(O)(CH<sub>3</sub>), NH- and CH<sub>3</sub>C(O)NHCH(CH<sub>4</sub>CH(CH<sub>3</sub>)).
- 18. A compound of claim 1, selected from the group consisting

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wherein R. is a PEG residue and D in selected from the resum consisting of

where B is a residue of an earline or a hydroxyd- containing drag.

- A compared of claim 15, wherein B is a residue of a member of the group consisting of: dumonablein, dozenubeln; p-eminoemiline masterd, melphalan, Ara-C (cytorian arabicosido), leocine-Ara-C, and generablese
- 70. A multiod of treatment, comprising administering to a manual to need of such treatment as effective amount of a compound of claim 1, wherein D, is a residue of a biologically solive mosety.
- A method of trestreon, comprising administering to a marrent in need of such treatment an effective amount of a compound of claim 18.

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#### 22. The compound of claim I, wherein Ar comprises the formula:

wherein  $R_{tt}$  and  $R_{tt}$  are individually schedul from the group consisting of hydrogen,  $C_{tt}$  allysis,  $C_{tt}$  are consistent of hydrogen, and the properties of th

## 21. The compound of claim 22, wherein $R_{ij}$ and $R_{ijklk}$ are each M or $CH_{j\nu}$

#### A method of preparing a polymer conjugate, comprising: reacting a compound of the formula (VIII);

(v) and (i) ero independently 0 or a positive integer up to about

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and L, are independently selected bifunctional linkers;

N<sub>s</sub> are independently selected from the group consisting of O, S and NR<sub>s</sub>;

R<sub>s,1</sub> are independently selected from the group consisting of O<sub>s</sub> S and NR<sub>s</sub>;

C<sub>s</sub>, aNyl. (C<sub>s</sub>) a threshold allyle (C<sub>s</sub>) exclude from the group consisting of lyphogen,

C<sub>s</sub>, aNyl. (C<sub>s</sub>) a threshold allyle (C<sub>s</sub>) exclude flow, for excluding all Nyl. (C<sub>s</sub>) asharized cyclosulysts, aryle, admitted only (C<sub>s</sub>) asharized cyclosulysts, aryle, admitted C<sub>s</sub> between the constant of the constant of

Ar is a mouthy which when included in Formula (I) forms a multi-substituted contrib hydrocorbon or a multi-substituted bettercoyelic group; and

B', is a residue of a hydroxyl- or an amma-containing moisty; with a compaund of the formula (DC):

whe



E., ure independently H, E. e

<del>([)</del>!--

 $D_2$  and  $D_4$  we independently OH, a leaving group which is capable of resuling with an augmentated andre or hydroxyl or a terminal branching group;

R, is a polymeric residue;

R, is a polymeric residu Y<sub>1</sub> is O, S or NR<sub>4</sub>;

M to O, S or NR<sub>c</sub>;

(a) is more or one;

(m) is 9 or a positive integer;

(n) and (p) are independently 0 or a positive integer:  $Y_{a\,a} \mbox{ are independently O. S or } NR_{a\,a} \mbox{ and }$ 

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 $R_{\nu_{em}}$  are independently actioned from the group consisting of hydrogen,  $C_{\nu_{em}}$  shipts.  $C_{\nu_{em}}$  branched allyds,  $C_{\nu_{em}}$  evaluating the  $C_{\nu_{em}}$  descinated onlyds,  $C_{\nu_{em}}$  and the probability of the particular of  $C_{\nu_{em}}$  between  $C_{\nu_{em}}$  branched and  $C_{\nu_{em}}$  between  $C_{\nu_{em}}$  branched and  $C_{\nu_{em}}$  between  $C_{\nu_{em}}$  branched and  $C_{\nu_{em}}$  between  $C_{\nu_{em}}$  branch and  $C_{\nu_{em}}$  between  $C_{\nu_{em}}$  branch and  $C_{\nu_{em}}$  between  $C_{\nu_{em}}$  and  $C_{\nu_{em}}$  between  $C_{\nu_{em}}$  branch and  $C_{\nu_{e$ 

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(4) Hydrological strate (4)
(5) Hydrological strate (4)
(6) Hydrological strate (4)
(7) Hyd

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# (国際調査報告)

	INTERNATIONAL SEARCH REPO	ora:	PCT/CSOL/or	plication No. Teo			
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	Minimum decumentation searched (classification system followed by elsewhorene symbols)						
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	ista basa consultad during the international acredi i, assent sures, polysterif, respignos, branchif, comp		where practicable	e, aconch strene modij			
C. DOCUMENTS CONSIDERED TO BE RELEVANT							
Category*	Circies of document, with indicator, where appropriate, of the relevant paragrap			Referent to claim No.			
У	GREENWALD et al.; Drug delivery systems based on trimethyl lock lactonization: Poly(ethylent glycol) Prodrugs of amino-containing compounds; 2000, Chem Abstract 132: 227266			1-24			
Y	GREENWALD et al: "TriaByl-lock-facilitated polymetric prodrugs 1-24 of amino-containing biosotive agents"; 1999; Chem Abstract 131; 22540						
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DYTERNATIONAL SEARCH	REPORT	Exercisional application No. PCT/L200/04180				
A. CLASSIFICATION OF SUBJECT MATTER. US Ct						
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 【手続補正書】
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 【補正方法】変更
 【補正の内容】
 【特許請求の範囲】
 【請求項1】
 【化1】
 (I)
 1式中、
 R は高分子残基であり;
Y, はO、SまたはNR, であり;
```

 $\begin{array}{c|c}
 & Y_2 \\
 & Y_2 \\
 & P_2 \\
 & P_3
\end{array}$ 

見は 【化2】

であり;

E\_aは独立に、H、Eまたは

MはO、SまたはNR、であり;

# [化3]

$$\begin{array}{c}
\begin{pmatrix}
R_{9} \\
C
\end{pmatrix} & \downarrow \\
C \\
R_{9}
\end{pmatrix} & \downarrow D_{2}$$

#### であり:

(a)は0または1であり;

(m)は0または正の整数であり;

(n)および(p)は独立に、Oまたは正の整数であり;

 $Y_{2-3}$ は独立に、O、SまたはNR<sub>10</sub>であり;

 $R_{-10}$ は独立に、水素、 $Q_{-6}$ アルキル、 $Q_{-1}$ ,分枝鎖アルキル、 $Q_{-6}$ シクロアルキル、 $Q_{-6}$  置換アルキル、 $Q_{-6}$  置換アルキル、 $Q_{-6}$  で 選換アルキル、 $Q_{-6}$  で  $Q_{-6}$   $Q_{-6}$  で  $Q_{-6}$ 

D<sub>2</sub> およびD<sub>2</sub> は独立に、OH、

# [1½4]

## (式中、

(v)および(t)は独立に、0または約6までの正の整数であり; JはNR,,または

## 【化5】



## であり;

L, およびL, は独立に選択された二官能性リンカーであり:

Yanは独立に、O、SおよびNRaからなる群から選択され;

R<sub>11-14</sub>は独立に、水素、C<sub>1-6</sub>アルキル、C<sub>3-12</sub>分枝鎖アルキル、C<sub>3-8</sub>シクロアルキル、C 1-6 置換アルキル、Ca-a 置換シクロアルキル、アリール、置換アリール、アラルキル、Ca-。ヘテロアルキル、雷操C。ヘテロアルキル、C。アルコキシ、フェノキシおよびC。へ テロアルコキシからなる群から選択され;

Arは式(I)に含まれる場合に多置換芳香族炭化水素または多置換複素環基を形成する成 分であり:

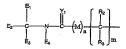
B, およびB, は独立に、脱離基、OH、ヒドロキシル基含有成分またはアミン基含有成分の 残基からなる群から選択される)

または末端分枝基であるし

で表される化合物。

【請求項2】

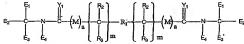
R, が水素、NH, 、OH、CO, H、C, 。基および [14:6]



からなる群から選択されるキャッピング基Aをさらに含んでなる、請求項1に記載の化合 物。

# 【請求項3】

式: [48.7]



で表される、請求項2に記載の化合物。

【請求項4】

上記末端分枝基が式:

# [化8]

# (式中、

E ., 12 [化9]



# であり;

E36-38は独立に、H、E35または 【化10】



## であり;

(n)および(p)は独立に、0または正の整数であり;

Y, , は独立に、O、SまたはNR, 。であり;

 $R_{e-10}$ は独立に、水素、 $C_{1-e}$ アルキル、 $C_{3-12}$ 分枝鎖アルキル、 $C_{3-e}$ シクロアルキル、 $C_{3}$ -。置換アルキル、C<sub>3-8</sub>置換シクロアルキル、アリール、置換アリール、アラルキル、C<sub>1-6</sub> ヘテロアルキル、置換C<sub>-6</sub>ヘテロアルキル、C<sub>-6</sub>アルコキシ、フェノキシおよびC<sub>-6</sub>ヘテ ロアルコキシからなる群から選択され;

D',およびD',は独立に、OH、

# 【化11】

# または 【化12】

1式中、

(v)および(t)は独立に、0または約6までの正の整数であり;

しおよびしは独立に選択された二官能性リンカーであり;

Y<sub>4-7</sub>は独立に、O、SおよびNR<sub>4</sub>からなる群から選択され;

R<sub>1-14</sub>は独立に、水素、C<sub>-6</sub>アルキル、C<sub>-12</sub>分枝鎖アルキル、C<sub>-6</sub>シクロアルキル、C<sub>-6</sub>で接アルキル、C<sub>1-6</sub>置接アルキル、C<sub>1-6</sub>では、アリール、置接C<sub>-6</sub>へテロアルキル、C<sub>1-6</sub>アルコキシ、フェノキシおよびC<sub>-6</sub>へテロアルコキシからなる群から選択され、

Arは式(I)に含まれる場合に多置換芳香族炭化水素または多置換複素環基を形成する成分であり;

B.およびB.は独立に、脱離基、OH、ヒドロキシル基含有成分またはアミン基含有成分の 残基からなる群から選択され;

E ., 13

$$\begin{array}{c|c}
 & \text{(1k 1 3)} \\
 & \text{C} & \text{C} \\
 & \text{C} & \text{C} \\
 & \text{R}_{7} & \text{C} \\
 & \text{R}_{2} & \text{C} & \text{C} \\
 & \text{R}_{2} & \text{C} & \text{C} \\
 & \text{R}_{2} & \text{C} & \text{C} & \text{C}
\end{array}$$

であり;

E<sub>46-48</sub>は独立に、H、E<sub>4</sub>,または 【化14】



(式中、 D",およびD",は独立に、OH、 【化15】

または 【化16】

である)

である」である

で表される、請求項1に記載の化合物。

【請求項5】

Y, が0である、請求項3に記載の化合物。

```
【請求項6】
```

R<sub>1</sub>がポリアルキレンオキシド残基を含んでなる、請求項1に記載の化合物。 【清求項7】

R がポリエチレングリコール残基を含んでなる、請求項6に記載の化合物。

【請求項8】

R、がポリエチレングリコール残基を含んでなる、請求項3に記載の化合物。 【請求項9】

# Rが

-C(=Y, )-(CH, ), -0-(CH, CH, O), -A,

-C(=Y, )-Y, -(CH, ), -0-(CH, CH, 0), -A,

-C(=Y<sub>6</sub>)-NR<sub>6</sub>, -(CH<sub>6</sub>), -O-(CH<sub>6</sub>CH<sub>6</sub>O), -A

-(CR, , R, , ), -0-(CH, ), -0-(CH, CH, O), -A.

-NR, , -(CH, ), -0-(CH, CH, O), -A, -C(=Y, )-(CH, ), -O-(CH, CH, O), -(CH, ), -C(=Y, )-,

-C(=Y, )-Y, -(CH, ), -0-(CH, CH, O), -(CH, ), -Y, -C(=Y, )-,

-C(=Y<sub>6</sub>)-NR, ,-(CH<sub>2</sub>),-O-(CH, CH, O), -(CH, ),-NR, ,-C(=Y<sub>6</sub>)-,

-(CR, R,,),-0-(CH,),-0-(CH, CH, O), -(CH,),-0-(CR, R,,),-, \$3 L U -NR, , -(CH, ), -0-(CH, CH, O), -(CH, ), -NR, , -

(式中、 YaおよびY,は独立に、O、SまたはNR,であり;

# ×は重合度であり;

R<sub>2</sub>, R<sub>2</sub>, およびR<sub>2</sub>, は独立に、H、G、アルキル、G、1, 分枝鎖アルキル、C、シクロア ルキル、C. - 。置換アルキル、C. - \*置換シクロアルキル、アリール、置換アリール、アラル キル、C.-6ヘテロアルキル、置換C-6ヘテロアルキル、C.-6アルコキシ、フェノキシおよ び「、こ。ヘテロアルコキシからなる群から選択され;

eおよびfは独立に、0、1、または2であり; かつ

Aはキャッピング基である)

からなる群から選択される、請求項6に記載の化合物。

# 【請求項10】

R.が-0-(CH, CH, O), を含んでなり、かつxは重量平均分子量が少なくとも約20,000である ような正の整数である、請求項9に記載の化合物。

## 【請求項11】

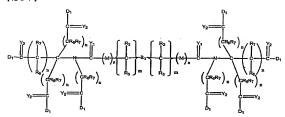
R. の重量平均分子量が約20,000~約100,000である、請求項3に記載の化合物。

# 【請求項12】

R. の重量平均分子量が約25,000~約60,000である、請求項3に記載の化合物。 【請求項13】

#### 式

# 【化17】



で表される、請求項3に記載の化合物。

【請求項14】

D<sub>4</sub>が 【化18】

である、請求項13に記載の化合物。

【請求項15】

D<sub>1</sub> が

[/L 1 9 ]

である、請求項13に記載の化合物。

【請求項16】

L, が(OH, OH, O), である、請求項1に記載の化合物。

【請求項17】

L, が-CH, -、-CH(CH, )-、-CH, C(O)NHCH(CH, )-、-(CH, ), -、-CH, C(O)NHCH, -、-(CH, ), -NH-C(O)(CH, ), NH-および-CH, C(O)NHCH(CH, CH(CH, ), )-からなる群から選択される、請求項 1 に記載の化合物。

【請求項18】

[化20]

# および 【化21】

|式中、 R<sub>s</sub>はPEC残基であり、かつDは

# [化22]

# および 【化23】

### (式中、

Bはアミンまたはヒドロキシル基含有薬物の残基である)

からなる群から選択されるし

からなる群から選択される、請求項1に記載の化合物。

【請求項19】

LMGペパッ] あがダウノルビシン、ドキソルビシン; p-アミノアニリンマスタード、メルファラン、A ra-C(シトシンアラビノシド)、ロイシン-Ara-C、およびゲムシタビンからなる群のメンバ 一の残禁である、講宗項 1 8 に記載の化合物。

【請求項20】

治療が必要な哺乳類に投与するための、有効量の請求項1に記載の化合物(式中、D,は生物学上活性な成分の残基である)を含む医薬組成物。

【請求項21】

治療が必要な哺乳類に投与するための、有効量の請求項18に記載の化合物を含む医薬 組成物。

【請求項22】

Arが式:

#### (式中、

R<sub>11</sub>およびR<sub>18-20</sub>は独立に、水素、C<sub>1-6</sub>アルキル、C<sub>3-12</sub>分枝鎖アルキル、C<sub>3-8</sub>シクロア ルキル、Cas置換アルキル、Cas置換シクロアルキル、アリール、置換アリール、アラル キル、C.sヘテロアルキル、置換C.sヘテロアルキル、C.sアルコキシ、フェノキシおよ びて、-。ヘテロアルコキシからなる群から選択される)

で表される、請求項1に記載の化合物。

### 【請求項23】

R<sub>1</sub>, およびR<sub>18-20</sub>が各々、HまたはCH<sub>1</sub>である、請求項22に記載の化合物。

【請求項24】

高分子複合体の製造方法であって、 式(VIII):

## (式中、

(v)および(t)は独立に、0または約6までの正の整数であり;

JはNR,,または 【化26】

## であり;

L,およびL,は独立に選択された二官能性リンカーであり;

Y<sub>4-5</sub>は独立に、O、SおよびNR<sub>17</sub>からなる群から選択され;

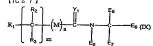
R1-17は独立に、水素、C1-6アルキル、C3-1,分枝鎖アルキル、C1-8シクロアルキル、C 1-6置換アルキル、C3-6置換シクロアルキル、アリール、置換アリール、アラルキル、C1-«ヘテロアルキル、置換C.-。ヘテロアルキル、C.-。アルコキシ、フェノキシおよびC.-。ヘ テロアルコキシからなる群から選択され;

Arは式(I)に含まれる場合に多置換芳香族炭化水素または多置換複素環基を形成する成

分であり;かつ

B', はヒドロキシルまたはアミン基含有成分の残基である) で表される化合物と、式(DX):

[1k.27]



(式中、

E,は 【化28】



であり;

E<sub>6-8</sub>は独立に、H、E<sub>5</sub>または 【化29】



75 t 10 .

D,およびD,は独立に、OH、保護されていないアミンまたはヒドロキシルと反応しうる脱離基、または末端分枝基であり;

R<sub>1</sub>は高分子残基であり;

Y, はO、SまたはNR, であり, MはO、SまたはNR, であり;

(a)は0または1であり;

(m)は0または正の整数であり;

(n)および(p)は独立に、0または正の整数であり;

Y<sub>2-1</sub>は独立に、O、SまたはNR<sub>1</sub>。であり;かつ

 $R_{-10}$ は独立に、水素、 $G_{-6}$ アルキル、 $G_{-12}$ 分枝鎖アルキル、 $G_{-10}$ シクロアルキル、 $G_{-6}$ 電換アルキル、 $G_{-6}$ 電換アルキル、 $G_{-6}$ でデロアルキル、 $G_{-6}$ でデロアルキル、 $G_{-6}$ でデロアルキル、 $G_{-6}$ でデロアルキル、 $G_{-6}$ でデロアルキル、 $G_{-6}$ でデロアルコキシ、フェノキシおよび $G_{-6}$ へテロアルコキシからなる群から選択される)

で表される化合物とを、高分子複合体を生成させるのに十分な条件下で反応させることを含んでなる、上記方法。